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CORRECTIONS

Volume 39, 1961

Page 1861, line 21; page 1862, line 19; page 1863, lines 2 and 14. The reference "(2)" in the above-mentioned lines should read "(3)".

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RADIATION CHEMISTRY OF CYCLOHEXANE

IV. PRIMARY PRODUCT YIELDS IN THE IRRADIATION OF CYCLOHEXANE[1]

P. J. DYNE AND J. A. STONE

ABSTRACT

The radiolysis of cyclohexane has been studied at low total doses and initial G values have been determined. Ninety-nine per cent of the evolved hydrogen has been accounted for in hydrogen-deficient products. Cyclohexene, bicyclohexyl, and cyclohexyl-hexene-1 have been identified as primary reaction products. Cyclohexyl-cyclohexene has been identified as a secondary reaction product. The use of high irradiation doses has been shown to lead to decreases in the initial G values of all primary products.

INTRODUCTION

A common feature of the reported product yields in the radiolysis of cyclohexane is the discrepancy between the hydrogen yield and the sum of the yields of hydrogen-deficient products—principally bicyclohexyl and cyclohexene (1, 2, 3, 4). In all cases the total yield of hydrogen-deficient products is not great enough to account for the observed hydrogen yield. It is generally assumed that high molecular weight products are formed which have remained undetected. There are also disagreements on the identity and yield of some of the minor products.

Cyclohexene, a major product, reduces $G(H_2)$ and is itself destroyed in the radiolysis (5, 6). It follows that accurate initial G values for any product can only be obtained by working at low conversions and by extrapolations to zero dose, thus avoiding the complications of secondary reactions.

This paper describes analytical techniques for the identification and analysis of products at conversion of less than 0.01%. At these low conversions the primary products appear to be cyclohexene, bicyclohexyl, and 6-cyclohexyl-hexene-1. A good hydrogen balance is obtained, all but 1% of the hydrogen being accounted for.

EXPERIMENTAL

Materials

Fisher Scientific Company Spectrograde cyclohexane was used as received. Gas–liquid chromatography showed three small impurity peaks before the main cyclohexane peak, but neither the sizes nor the shapes of these peaks were altered by γ-radiolysis. Cyclohexene (Eastman) was used as a solute.

Preparation of Samples

The 20-ml samples were contained in Pyrex tubes, 2.5 cm in diameter and 25 cm long, each equipped with a break-tip seal and a constricted side arm. The samples were pipetted

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Contribution from Research Chemistry Branch, Atomic Energy of Canada Limited, Chalk River, Ontario. Issued as A.E.C.L. No. 1356.

into the tubes and were then degassed by the freeze–thaw technique. When the residual pressure was less than 5×10^{-6} mm, the sample tubes were sealed off at the constriction. The samples containing solute were made up in bulk and pipetted out as required.

Irradiation of Samples

The samples were irradiated at 22° C by Co-60 γ-rays. Dose rates were determined with the Fricke dosimeter, taking $G(Fe^{+++}) = 15.5$. Two irradiation facilities were used with dose rates of 4.8×10^{20} ev/liter minute, and 2.6×10^{19} ev/liter minute for cyclohexane at 22° C.

Product Analysis

The irradiated sample tubes were attached to a vacuum line and their contents frozen with liquid nitrogen. The gaseous products volatile at −196° C were then taken off with a Toepler pump and their volume measured with a McLeod gauge, the samples being thawed and refrozen to make sure that all the gas had been collected. Hydrogen was diffused through a heated palladium thimble, and the volume of the residual gas measured. In all cases it was found that this residue amounted to less than 1% of the initial volume. This was confirmed by mass spectral analysis of the collected gas.

The liquid products were analyzed by gas–liquid chromatography. Cyclohexene was determined using a 4-meter column of 3-mm internal diameter, containing firebrick on which was deposited 30% by weight of a silver nitrate/$\beta\beta'$ oxydipropionitrile mixture as the stationary phase. The column was at room temperature, the sample injection end being at a slightly higher temperature. The results were checked quantitatively by infrared analysis, using the 717-cm^{-1} cyclohexene band. Products of higher molecular weight than cyclohexane were separated on a 2.5 meter long, 2.5-mm internal diameter column containing 0.1% by weight of Apiezon-L grease on 200-micron diameter glass beads. This column, with a very low concentration of L-grease, gave better separations than a conventional column containing more grease. The more heavily loaded column must be used at a higher temperature to obtain the same separations in a comparable time. With the minimum amount of L-grease, the tailing of cyclohexane was greatly reduced, the less volatile components being eluted at lower temperatures with improved resolution. This column was at a fixed temperature for quantitative work but was temperature programmed for qualitative work.

A simple hydrogen flame detector (7) was used, together with a split-stream device after the column. The output from the detector was fed through the 10^9-ohm input resistor of an electrometer. Ten-λ samples of the irradiated material, without previous concentration, were injected directly onto the columns, the whole sample being passed through the detector. A new calibration curve was used for each series of analyses, standards and unknowns being run alternately. No standards were available for products other than cyclohexene and bicyclohexyl so their concentrations were obtained from measured peak areas, the peak area being assumed to be proportional to molar concentration.

A Consolidated 21-130 Mass Spectrometer was connected to the outlet of the chromatographic column by means of a heated, stainless steel capillary tube. Approximately 90% of the eluted sample passed through the detector, whilst the remaining 10% flowed through the capillary past a gold leak in the spectrometer sample introduction system. The capillary introduced a delay of the order of 5 seconds between the appearance of a chromatographic peak and the initial appearance of the mass spectrum due to the same component. The spectra were recorded on a recording oscillograph, the time taken to scan from mass

26 to mass 200 being of the order of 1 minute. Interpretable spectra were obtained when the desired component was present in the chromatographic eluent at a concentration of about 100 p.p.m. To obtain this concentration for the components which were present in very small amounts in irradiated samples, the following procedure was employed. A large sample (~0.5 ml) of irradiated material was injected, 20 λ at a time, onto the narrow L-grease column. Cyclohexane, which comprised 99.9% of the solution, was eluted rapidly at room temperature, leaving the higher-boiling components still at the column inlet. When sufficient material had been deposited on the column the temperature was raised gradually so that a good chromatographic separation was achieved and the mass spectra obtained. To ensure a rapid clearing of the spectrometer inlet system, and therefore no enhancement of the background spectrum, the temperature of the inlet system was maintained at 200° C and that of the spectrometer ion source at 250° C.

Samples from the chromatographic column were trapped out in micro infrared cells cooled in a solid CO_2/acetone mixture. The spectra of these samples were obtained on a Perkin–Elmer model 21 machine equipped with a beam condenser.

RESULTS

1. Pure Cyclohexane

The variation of $G(H_2)$ with dose, at a dose rate of 4.8×10^{20} ev/liter minute, is shown in Fig. 1. Each point on this curve represents the result of one measurement except for the initial G value, which was obtained from a series of measurements extrapolated to zero dose. At low doses a sharp decrease in $G(H_2)$ with increasing dose occurs, but at

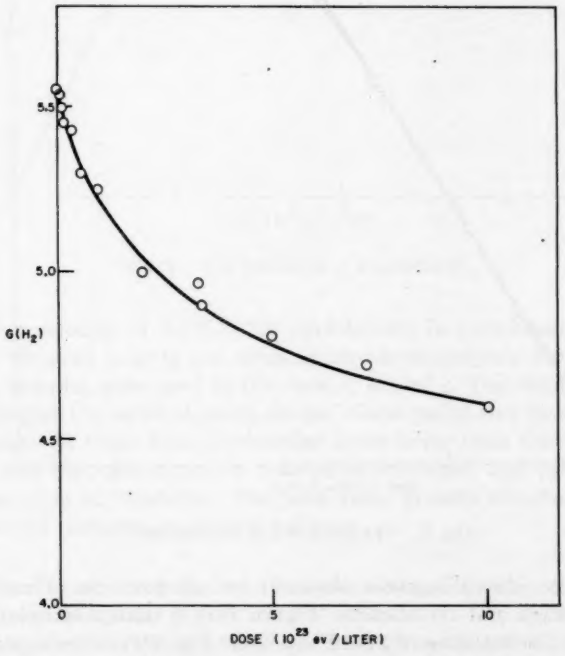

FIG. 1. The variation of $G(H_2)$ with total dose.

higher doses the rate of decrease becomes smaller. The initial G value is 5.55. The decrease is clearly non-linear with dose. At the lower dose rate of 2.6×10^{19} ev/liter minute a similar decrease in $G(H_2)$ with dose was recorded. The initial G value was the same within experimental error, but at the lower dose rate the decrease was more rapid with increasing dose. Figure 1 represents a refinement on previously published data (3, 5).

The formation of cyclohexene as a function of dose is shown in Fig. 2. The initial G value is 3.27. At the higher doses shown in the figure the G value is beginning to decrease. A similar curve for bicyclohexyl is shown in Fig. 3. The initial G value is 1.95, and again at the higher doses this value decreases.

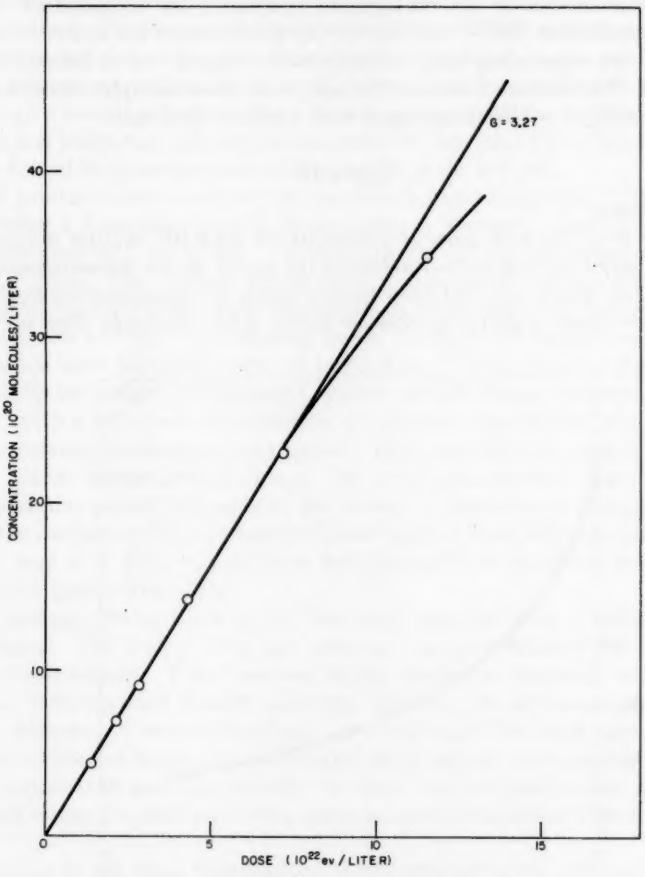

FIG. 2. The formation of cyclohexene.

Figure 4 shows the chromatograms obtained for all products of molecular weight higher than cyclohexane and cyclohexene. Figure 4(a) is from a sample of pure cyclohexane irradiated to the low dose of 2×10^{22} ev/liter; Fig. 4(b) is from pure cyclohexane irradiated to the much higher dose of 2×10^{24} ev/liter, and 4(c) is the chromatogram

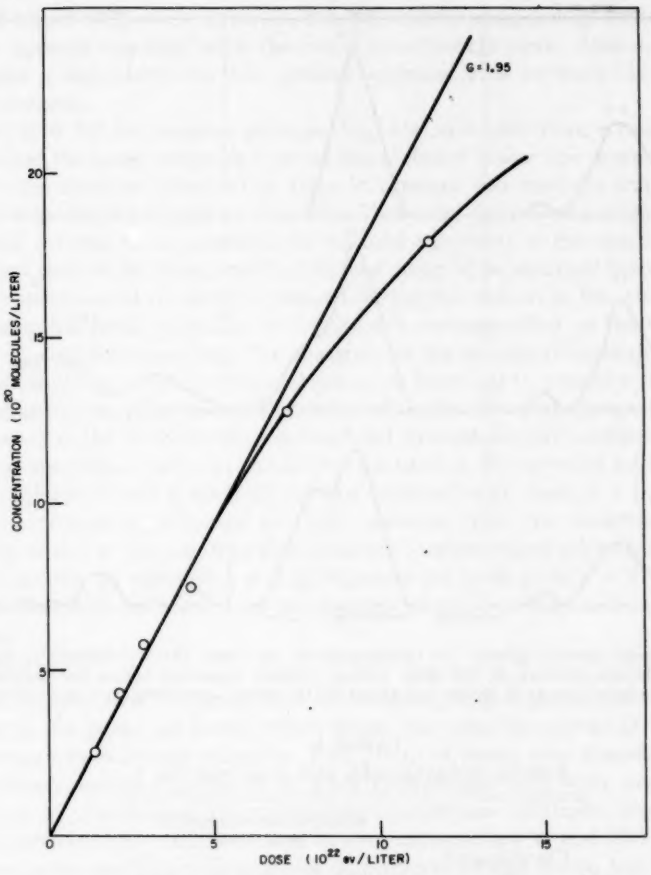

FIG. 3. The formation of bicyclohexyl.

obtained from a solution of $4.5\times10^{-2}M$ cyclohexene in cyclohexane irradiated to 10^{23} ev/liter. Only the peak heights and areas in one chromatogram should be compared, as different-sized samples were used in the runs *a*, *b*, and *c*. The column was temperature programmed to give the series of peaks shown. These peaks may be conveniently divided into three groups, (i) those having retention times lower than that of bicyclohexyl, (ii) those with almost the same retention time as bicyclohexyl, and (iii) those with greater retention times than bicyclohexyl. The peak areas in each chromatogram are given in Table I in terms of percentages of the total area.

Group i

For pure cyclohexane irradiated to a low total dose, Fig. 4(*a*), the estimated *G* value for all products in this group is 0.27.

An infrared spectrum of a trapped sample from group i showed an absorption band at 1634 cm^{-1} corresponding to the C=C stretching frequency of hexene-1. The mass spectrum

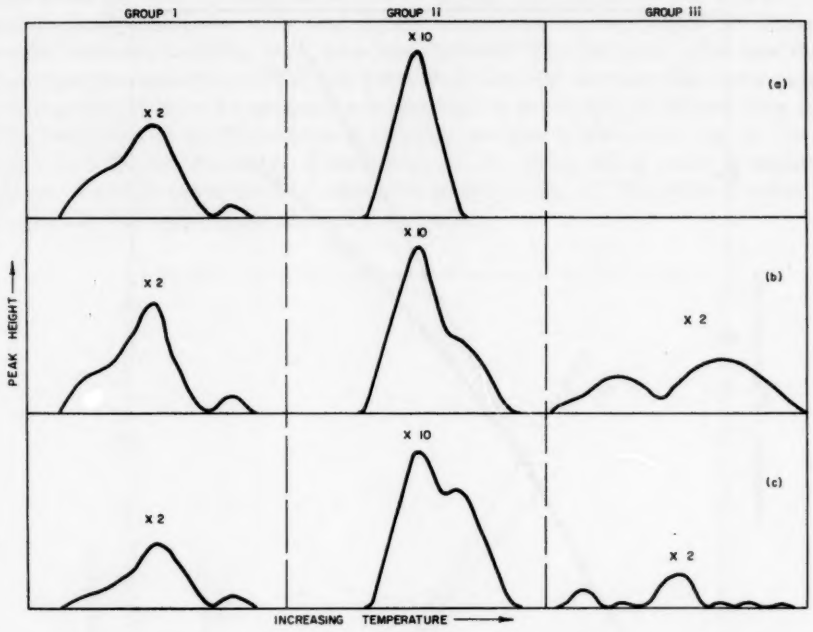

FIG. 4. Gas–liquid chromatograms: (*a*) cyclohexane at low dose; (*b*) cyclohexane at high dose; (*c*) cyclohexane–cyclohexene mixture at low dose. Group i, peaks appearing before the bicyclohexyl peak; group ii, the bicyclohexyl group of peaks; and group iii, the peaks appearing after bicyclohexyl.

TABLE I

Relative chromatographic peak areas from Fig. 4

Chromatogram No.	Relative chromatographic peak areas		
	4(*a*)	4(*b*)	4(*c*)
Group i	12	14	8.5
Group ii	88	70	82
Group iii	0	16	9.5

showed a parent peak at $m/e = 166$, together with fragment ions associated with both cyclohexyl and hexenyl groups. Unlike the spectrum of bicyclohexyl, the most intense peak of which is at $m/e = 82$, the peak at $m/e = 83$ was found to be the largest. This would suggest that a cyclohexane molecule substituted with a straight chain of mass 83 was present. Since the infrared spectrum showed that a cyclohexene group was not present the double bond must be in the side chain. The main chromatographic peak in group i is, therefore, most probably 6-cyclohexyl-hexene-1.

Group ii

Figure 4(*a*) shows that at very low doses a single peak is obtained. This peak is symmetrical with no sign of any other substance present. A symmetrical peak was obtained no matter how the column conditions were varied, showing that, in all probability, the

identification of this peak as due to a single component, bicyclohexyl, was justified (see below). At higher total doses, however, this was not the case, as Fig. 4(*b*) shows. A second peak now appears together with the main bicyclohexyl peak, demonstrating that at higher doses a secondary reaction product appears. This we have identified as cyclohexyl-cyclohexene.

For a $4.5\times10^{-2}M$ cyclohexene solution, Fig. 4(*c*), a double peak is observed. The first maximum has the same retention time as bicyclohexyl whilst the second corresponds in position to the shoulder observed in 4(*b*). At attempt was made to trap the compound associated with the main peak in Fig. 4(*a*). However, the concentration of this product was too low for this to be possible. An infrared spectrum of the compound associated with the first part of the main peak in 4(*b*) was found to be identical with that of bicyclohexyl. The spectrum of the sample trapped during the elution of the whole peak showed a new absorption band appearing at 1642 cm^{-1}, corresponding to the C=C stretching frequency in a cyclohexene ring. The spectrum of the sample trapped during the elution of the main double peak of 4(*c*) showed the same band but in greater strength. From the chromatographic retention time and the infrared results, it would appear that this product, which appears as the radiation dose is increased, is a substituted cyclohexene.

The mass spectrum confirmed the above conclusions. The product provisionally identified as bicyclohexyl had a spectral pattern identical with that of a pure sample. The cyclohexyl-cyclohexene, although not fully resolved from the bicyclohexyl, showed a parent peak at $m/e = 164$, together with fragment ions associated with cyclohexyl groups at $m/e = 83$ and 82. In addition a strong fragment ion peak at $m/e = 81$ was deduced to be the cyclohexenyl ion formed by the rupture of the two ring molecule at the central C—C bond.

Group iii

This group contains the peaks due to compounds of higher molecular weight than bicyclohexyl. No peaks are found at low doses, but some do appear at higher doses and in cyclohexane–cyclohexene mixtures. This group of peaks may therefore be associated with secondary reaction products in pure cyclohexane and with products involving the reaction of cyclohexene in cyclohexane–cyclohexene mixtures. No correlation was attempted between the products found in chromatograms 4(*b*) and 4(*c*).

Attempts were made to trap samples of products in this group but without success. Mass spectra showed that cyclohexyl groups were present but no parent peaks could be detected.

2. Cyclohexane–Cyclohexene Mixtures

Samples of a $4.5\times10^{-2}M$ cyclohexene solution were irradiated at the higher dose rate for varying doses up to 10^{23} ev/liter. The gaseous product volatile at $-196°$ C was more than 99% hydrogen. The initial $G(H_2)$ was 4.76. This value was constant over the dose range studied.

The determination of a G value for the production of cyclohexene was difficult. A value of 0.6 ± 0.3 was obtained. The large error was due to the fact that at the doses used only a small change in cyclohexene concentration occurred.

G(bicyclohexyl) could not be determined since complete resolution from the peak assigned to cyclohexyl-cyclohexene could not be obtained. Both peak areas were measured together and the total area was calibrated against that for pure bicyclohexyl. A total G value of 1.3 was found. The sensitivity of the chromatographic detector for bicyclohexyl only was determined, and so the error involved in using this calibration was not

known. With the type of detector used the error is, however, probably small. By visual inspection of the peak shape (Fig. 4(*a*) group ii), it is seen that bicyclohexyl constitutes roughly 55% of the total area, which would correspond to a *G* value of 0.72.

The analyses for products in groups i and iii were less accurate. The *G* values obtained were 0.13 and 0.15 respectively.

DISCUSSION

The results obtained for the product yields in the radiolysis of pure cyclohexane by Co-60 γ-rays are summarized in Table II.

TABLE II

Initial *G* values for products in the irradiation of pure cyclohexane

Product	*G*	
Hydrogen	5.55±0.05	
Cyclohexene	3.27±0.06	Hydrogen equivalent = 5.49
Bicyclohexyl	1.95±0.06	
Cyclohexyl-hexene-1	0.27±0.05	

All these results were obtained by extrapolation to zero dose since it was shown that the *G* values of all products decrease with increasing dose. An excellent hydrogen balance has been obtained showing that in the initial stages of radiolysis, i.e. at very low doses, a simplicity of products is observed. No dienes or high molecular weight products are observed and indeed none need be invoked since there is no hydrogen deficit.

At higher doses complications arise. The *G* values of all the initial products decrease and secondary reaction products appear. Cyclohexyl-cyclohexene is one which has been definitely identified. High molecular weight products appear and the hydrogen deficit becomes greater. Dyne and Fletcher (6) have shown that, on prolonged radiolysis of cyclohexane, the cyclohexene reaches a limiting concentration when its rate of formation is equal to its rate of disappearance. In the present work it has been shown that the radiolysis of a mixture of cyclohexane and cyclohexene results in a decrease in G(cyclohexene) of about 2.7, but the decrease in $G(H_2)$ is only 0.9. This implies that the disappearance of cyclohexene is not brought about simply by the addition of hydrogen to the double bond, but some other reaction must be occurring. Since cyclohexyl-cyclohexene is a secondary product, some substitution at a saturated carbon atom takes place.

These results differ somewhat from those of Waight and Walker (8), who found lower yields of bicyclohexane and cyclohexene (1.6 and 2.4 respectively). The dose rate of their irradiation was about one tenth of the dose rate used here and, at the doses used (6×10^{22} ev/liter), it is consequently likely that their *G* values for these products would be significantly lower than the true initial value. We do not observe cyclohexyl-cyclohexene as a primary product.

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THE SEPARATION OF SMALL AMOUNTS OF THE PLATINUM METALS

1. THE COLORIMETRIC DETERMINATION OF RHODIUM AND ITS SEPARATION FROM IRIDIUM[1]

D. E. RYAN

ABSTRACT

A method for separating small amounts of rhodium from iridium is described. In 3 to 9 *M* hydrochloric acid solutions, the amber-to-red complex of bivalent rhodium with 4,5-dimethyl-2-mercaptothiazole is formed after reduction of tervalent rhodium with chromous or stannous chloride. Rhodium is quantitatively separated from iridium by chloroform extraction of this product; separation can be made in solutions that have been fumed with sulphuric acid if chromous chloride is used for the prior reduction of the rhodium. The complex, after removal of the chloroform, is dissolved in dilute hydrochloric acid, and the optical density of the resulting colored solution is measured.

INTRODUCTION

The separation of small amounts of the platinum metals still leaves room for improvement. Palladium can be separated by extraction of the dimethylglyoxime (1, 2), *p*-nitrosophenylamine (3, 4, 5), or 1-nitroso-2-naphthol (6) complexes into organic solvents; similar success is not so readily attained with small quantities of the other platinum metals.

The hydrous oxide procedure of Gilchrist and Wichers (7) provides a means of separating small amounts of platinum from similar quantities of iridium and rhodium (3, 5) and some success has been recorded for the separation of bivalent platinum complexes (1, 4, 8). Ammonium type salts $(R_4N)_2MX_6$, although satisfactory for determining small amounts of platinum metals in the quadrivalent state and for separating from commonly associated base metals, are of little use in the separation of the platinum metals themselves. Selective reduction by copper powder (9) has proved satisfactory for separating both milligram and microgram quantities of rhodium from iridium. Ion exchange methods have been used with varying success for separating microgram amounts of these metals (10). Where molecular chelate species are possible, solvent extraction offers a reasonable means of separation (11); such chelates are not probable for the platinum metals in the quadrivalent state (12). Distinct possibilities, however, lie in the principle of precipitating or extracting bivalent platinum metal complexes. Jackson (13) has quantitatively separated rhodium from iridium as an insoluble bivalent complex with thioacetanilide after reduction with chromous chloride; the method can be used for the determination of small amounts of iridium in rhodium but attempts to separate small quantities of rhodium from iridium by solvent extraction were unsuccessful. The following paper records the results of an investigation into the possibility of separating rhodium from iridium by extraction of a bivalent complex obtained after reduction.

Rhodium, in the bivalent state, reacts with 4,5-dimethyl-2-mercaptothiazole to give a colored complex that can be used for its determination (14). In the original paper the color was produced by boiling hydrochloric acid solutions of tervalent rhodium with excess reagent, the reagent itself acting to reduce the rhodium to the bivalent state; iridium produced a pale yellow color that caused some interference in the rhodium determination unless compensated in the reference cell; both the rhodium and iridium com-

[1]*Manuscript received June 15, 1961.*
Contribution from the Department of Chemistry, Dalhousie University, Halifax, Nova Scotia, and the Imperial College of Science and Technology, London, England; with financial assistance from the National Research Council, Ottawa, Canada.

plexes were extracted by organic solvents so that separation under these conditions is not possible. However, 4,5-dimethyl-2-mercaptothiazole, as many other thio compounds (13), reacts in the cold with rhodium when a reducing agent is added; the determination and separation of rhodium from iridium can be readily achieved by this means.

EXPERIMENTAL

In preliminary studies, a large number of compounds was investigated as possible reagents for reducing rhodium, at room temperature and in acid solution, from the tervalent to bivalent state. The compound was added to acidified rhodium chloride solutions containing 4,5-dimethyl-2-mercaptothiazole, and the development of the amber-to-red color of the complex of bivalent rhodium with this reagent taken as evidence of reduction. Only stannous chloride and chromous chloride, of the following compounds investigated, were useful for this purpose: ascorbic acid, cadmium, chromous chloride, ferrous sulphate, formic acid, *d*-glucose, hydrazine, hydrogen peroxide, hydroquinone, hydroxylamine, potassium hydrogen tartrate, sodium dithionite, sodium hypophosphite, sodium hyposulphite, sodium sulphite, stannous chloride, titanous chloride, zinc.

Reduction with Stannous Chloride

Stannous chloride, as is well known, reacts with acidified tervalent rhodium solutions to give a yellow or red color that is not extracted by chloroform; when it is added to rhodium solutions containing 4,5-dimethyl-2-mercaptothiazole, however, an amber-to-red color develops that is readily extracted by chloroform. The chloroform extract from iridium solutions similarly treated is colorless and free of iridium. Rhodium can be readily separated from iridium by this means in chloride solutions or from hydrochloric acid solutions containing sulphate. The optical densities for chloroform extract from samples containing the same quantity of rhodium are inconsistent. Reproducible results, and optical densities agreeing with those given by the original procedure with 4,5-dimethyl-2-mercaptothiazole (14), are obtained by removing the chloroform on the steam bath and dissolving the residue in a little ethanol and a diluted hydrochloric acid solution.

2-Mercaptothiazole, 2-mercaptothiazoline, 2-mercaptobenzoxazole, 4-methyl-2-mercaptothiazole, and 4-phenyl-2-mercapothiazole react also to give colored chloroform extracts. The extracts obtained for compounds substituted in the 4-position are amber-to-red in color but are yellow for the unsubstituted ones. Colorless chloroform extracts are obtained for 4-methyl-2-hydroxythiazole and 2-aminothiazole; the mercapto group is, therefore, essential to the reaction.

A Spekker photoelectric absorptiometer with an Ilford No. 601 filter (maximum transmittancy at 430 mμ) and a Cenco-Sheard-Sanford 'Photelometer' (filter No. C with maximum transmission at 435 mμ) were used to obtain the recorded data.

Reagents

4,5-Dimethyl-2-mercaptothiazole.—The reagent was made by the method of Buchman, Riems, and Sargent (15) and was recrystallized from 25% ethyl alcohol; a solution was prepared by dissolving 0.5 g in 100 ml of 50% ethanol.

Standard rhodium and iridium solutions.—These solutions were prepared by dissolving known weights of Matthey spectrographically pure ammonium chlororhodite and ammonium chloroiridate in dilute acid solutions.

Stannous chloride solutions.—The stannous chloride solution was a 10% solution of the dihydrate in 2 *N* hydrochloric acid.

Procedure

Solutions containing 0.04 to 0.3 mg of rhodium were transferred to separatory funnels and were made 3 to 9 *M* in hydrochloric acid by addition of the concentrated acid, and 1 ml of reagent solution was added for each 0.1 mg or less of rhodium expected to be present. The rhodium was reduced by adding 10 drops or more of stannous chloride, the solution then extracted with 15 ml of chloroform, and the organic phase transferred to a small beaker or flask; the aqueous layer was again extracted with 10 ml of chloroform. The combined extracts were evaporated on a steam bath and the residue was dissolved in 5 ml of ethanol, then boiled with 25 ml of 2.5 *M* hydrochloric acid. After being cooled, the solution was transferred to a 50-ml graduated flask and diluted to the mark with water. The optical density was measured in a 1-cm cell of an absorptiometer using a filter with maximum transmittancy of 430–435 mμ.

The optical densities obtained under various conditions are shown in Table I. These results are for 0.185 mg of rhodium, 2 ml of reagent, and a 1-cm cell; 10 drops of stannous chloride were used for reduction and the volume of the solution, before extraction, was approximately 20 ml for these samples.

TABLE I

Optical density of solutions of 0.185 mg of rhodium under various conditions

No.	Condition	Optical density
(1)	Hydrochloric acid present, 1.0 ml	0.384
(2)	" " " 5.0 ml	0.448
(3)	" " " 10.0 ml	0.446
(4)	" " " 15.0 ml	0.446
(5)	As in (2) + 2.0 ml of concentrated sulphuric acid	0.447
(6)	As in (2) + 5.0 ml of stannous chloride	0.444
(7)	As in (2) but stannous chloride added before reagent	0.425
(8)	As in (2) but 5.0 ml of reagent added	0.448

The data show that rhodium can be readily separated from 3 to 9 *M* hydrochloric acid solutions and determined by this procedure. Results are satisfactory in chloride solutions containing sulphuric acid, and excess stannous chloride or reagent cause no difficulty. The optical density for the same concentration of rhodium by the boiling procedure (14) is 0.447. Addition of stannous chloride before reagent causes some difficulty in removing the last traces of rhodium complex from the aqueous layer, and slightly low values for rhodium content are obtained. The procedure, using stannous chloride as reducing agent, gives unreliable results when applied to rhodium solutions that have been fumed with sulphuric acid; the chloroform extract from such solutions contains some yellow-colored product, in addition to the rhodium complex, the amount of which is dependent upon reagent, stannous chloride, and sulphuric acid concentration.

As in the original procedure (14) the colored solution obeys Beer's law over the range applicable for a 1-cm cell but the complex is not as stable. The optical density changed from 0.446 to 0.437 when the solution was kept in daylight in a closed container for 1 hour and decreased to 0.383 when the solution was left to stand overnight.

Separation of Rhodium from Iridium

Rhodium can be easily separated from iridium in chloride solutions; however, reagent is added to completely decolorize any quadrivalent iridium before the usual procedure is carried out. Results are shown in Table II.

TABLE II

Separation of rhodium from iridium

No.	Rh taken, mg	Rh found, mg	Ir present, mg	Approx. Ir:Rh ratio
1	0.037	0.036	3.7	100:1
2	0.037	0.039	30.2	800:1
3	0.052	0.053	1.0	20:1
4	0.052	0.054	4.5	85:1
5	0.074	0.073	7.4	100:1
6	0.130	0.129	5.2	40:1
7	0.150	0.150	2.2	15:1
8	0.150	0.153	16.0	100:1
9	0.185	0.181	4.0	20:1
10	0.185	0.185	25.0	140:1
11	0.185	0.185	33.0	180:1

A large excess of stannous chloride (5 ml), although unnecessary, was added for most of the results recorded in Table II; in results 3, 4, 6, obtained independently by H. M. Whitehead, 10–15 drops of stannous chloride were used for reduction.

Reduction with Chromous Chloride

The soluble complex formed on addition of chromous chloride to rhodium solutions containing 4,5-dimethyl-2-mercaptothiazole is extracted by chloroform from chloride solutions or from sulphate solutions containing hydrochloric acid; in chloride solutions the iridium complex is also extracted by chloroform. It is worth while noting that, although the iridium complex is extracted from freshly prepared ammonium chloroiridate solutions, no extraction of iridium occurs from the same solution after it has stood more than 2 weeks.

Procedure

Five milliliters of lithium sulphate:sulphuric acid reagent (13.5 g of Li_2SO_4 in 100 ml of concentrated H_2SO_4) was added to chloride solutions containing rhodium and iridium, and the solutions fumed to crystallization of lithium sulphate. The samples were diluted with 5 ml of water, heated to ensure complete dissolution, cooled to room temperature, and transferred to a separatory funnel. An approximately equal volume of concentrated hydrochloric acid was then added and freshly prepared chromous chloride solution (approximately 1 *N*) added dropwise to reduce rhodium and iridium. An excess of reagent was added, the solutions extracted with chloroform, and the procedure completed as described for stannous chloride. Results are given in Table III. The results show that rhodium can be separated from iridium, in solutions that have been fumed with sulphuric acid, by this procedure.

TABLE III

Separation of rhodium from iridium by chromous chloride procedure

Rh taken, mg	Rh found, mg	Ir present, mg
0.040	0.039	5.0
0.040	0.040	10
0.051*	0.051	1.0
0.051*	0.051	4.5
0.052*	0.054	9.0
0.078*	0.078	4.5
0.210	0.213	10
0.210	0.208	20

*These results were obtained independently by H. M. Whitehead, a member of this laboratory.

CONCLUSIONS

Rhodium can be separated and determined colorimetrically by extraction of the complex formed with 4,5-dimethyl-2-mercaptothiazole obtained after reduction with stannous chloride or chromous chloride. Rhodium can be separated from iridium in chloride solutions using stannous chloride as reducing agent; in solutions that have been fumed with sulphuric acid it is necessary to use chromous chloride to obtain satisfactory separation.

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THE EFFECT OF HYDROGEN CHLORIDE ON THE NEAR-INFRARED SPECTRUM OF NYLON[1]

P. LAROSE

ABSTRACT

Samples of oriented nylon film and filament were treated with anhydrous HCl and examined in the near-infrared region of 9000 to 3700 cm^{-1} with polarized light. The results are in agreement with previous observations made in the 3600–600 cm^{-1} region, and corroborate earlier evidence that HCl interacts with the peptide linkage. The disorienting effect of the HCl is also reflected in the spectrum of the treated specimens.

INTRODUCTION

The results of experiments on the effect of hydrogen chloride on the infrared spectrum of nylon in the region of 3600 to 600 cm^{-1} have been reported (5). The investigation has now been extended to the overtone region of 9000 to 3700 cm^{-1} since the spectrum of nylon in this region has been studied and the assignment of the bands discussed by several workers (1, 2, 3). It was hoped in this way to confirm our earlier results and possibly to provide additional data to support the assignment proposed for the various absorption bands.

EXPERIMENTAL

Oriented Zytel[2] film was prepared by casting onto glass from ethanol solution and stretching the film in hot water. Nylon 6 film[3] was also oriented by stretching it in hot water, while a sample of nylon 6.6 was examined in the form of a ribbon about 0.3 mm thick prepared by rolling a monofilament lengthwise. The samples were immersed in hexachlorbutadiene and the absorption spectra recorded on a Beckman DK2 spectrophotometer with light polarized by means of a Polaroid HR plastic filter. The samples were studied before and after treatment with anhydrous HCl and also after removal of the HCl *in vacuo*.

RESULTS

The various film and filament specimens yielded results which differed little in character so that no attempt will be made to distinguish between these various forms of nylon in discussing the results.

Figure 1 shows the spectrum of an oriented nylon film before treatment with HCl. It differs little from the spectrum reported by other workers with regard to dichroism and position of the absorption bands. Figure 2 is a portion of the absorption spectrum of a different sample of untreated nylon included here to emphasize a difference between the two vectors to be discussed. Figure 3 represents the spectrum of a sample treated with HCl. Figure 4 shows the spectrum of a thick sample after removal of the HCl, while Fig. 5 is for a thin sample also after removal of the HCl.

Because of form dichroism resulting from differences in the refractive indices of the nylon in directions parallel and perpendicular to the polymer chain direction, and because

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Contribution from the Division of Pure Chemistry, National Research Council, Ottawa, Canada.
Issued as N.R.C. No. 6535.
[2]*A copolymer of nylons 6, 6.6, and 6.10.*
[3]*The author is indebted to Dr. Stace of the British Nylon Spinners for this film.*

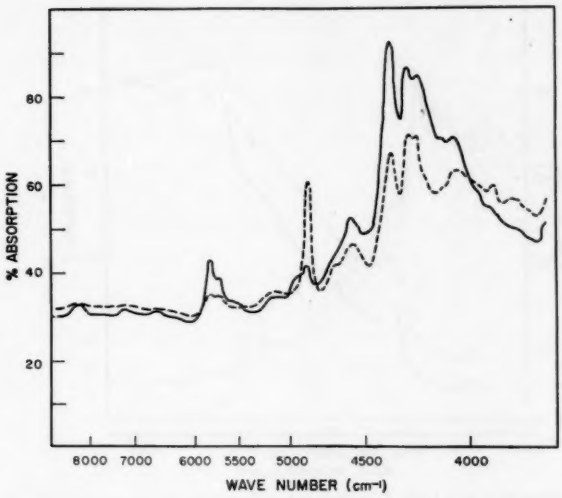

FIG. 1. Near-infrared spectrum of oriented nylon film. —— E vector perpendicular to direction of stretching. – – – E vector parallel to direction of stretching.

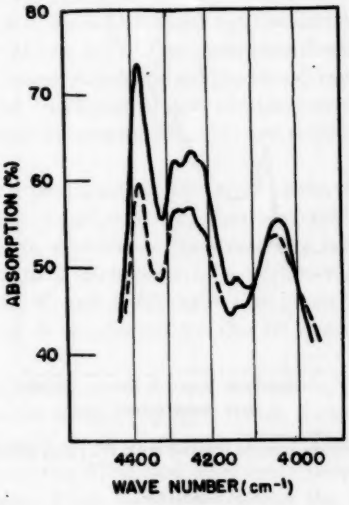

FIG. 2. As for Fig. 1.

of small differences in the transmission of the filter between its horizontal and vertical positions, the extent of dichroism was determined from a line drawn through the absorption minima. However, because of the uncertainties involved in such a method, no attempt has been made to express the dichroism quantitatively.

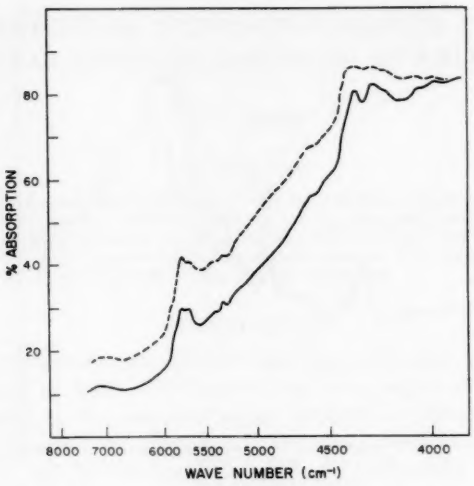

FIG. 3. Spectrum of nylon treated with HCl.

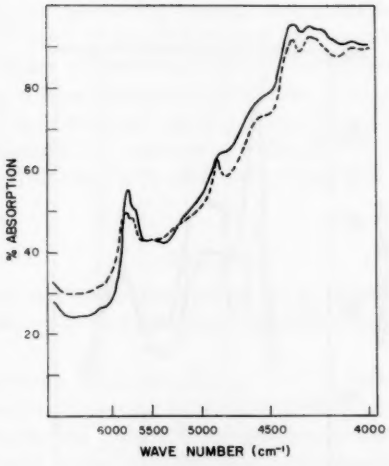

FIG. 4. Spectrum of thick nylon sample treated with HCl and subsequently evacuated.

DISCUSSION

If, as assumed in previous work (4, 5), the HCl acts on the —NH.CO— group, one would expect all overtones or combination modes involving this linkage to be affected by the HCl, whereas the bands due to the —CH_2— groups in the chain should not be so affected. A comparison of the spectra of the nylon treated with HCl with the spectrum of the untreated nylon shows that this was indeed the case. The changes produced by the HCl on the various bands are as follows.

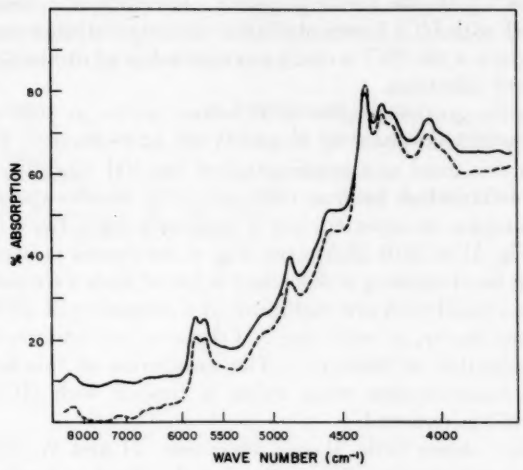

FIG. 5. Spectrum of thin nylon film treated with HCl and subsequently evacuated.

A weak band at 8240 cm^{-1} showing perpendicular (σ) dichroism in the untreated nylon is no doubt the same band as that reported at 8300 cm^{-1} by Hecht and Wood (3) (henceforth H and W) and at 8292 cm^{-1} by Glatt and Ellis (2) (G and E). It has been assigned as the third harmonic of the CH_2 stretching vibration at 2960 cm^{-1} (ν_a) or 2860 cm^{-1} (ν_s). The treated samples still show this band but the dichroism is absent (Fig. 5) because of the disorienting effect of the HCl. The disorientation is irreversible and is found in all HCl-treated samples. Some dichroism will be found remaining in the spectrum shown in Fig. 4. In this case the thickness of the sample prevented complete penetration of the HCl in the time allowed for absorption, and the residual effect is undoubtedly due to some unaffected nylon.

Another weak band at a frequency of 7020 cm^{-1} behaves like the 8240 cm^{-1} band. It does not seem to have been mentioned by other workers. It may be a combination of a $-CH_2-$ deformation mode with twice its stretching frequency ($2\nu+\delta$).

The 6520 cm^{-1} band with σ dichroism falls within the range 6300–6680 cm^{-1} given by H and W (3) for 2νNH. G and E (2) have also given this assignment to a 6523 cm^{-1} band. Being an NH band, it is affected by the HCl and is absent in the spectrum of the treated samples.

Two bands at 5760 and 5660 cm^{-1} show σ dichroism, particularly strong for the first one. These correspond to the 5800–5700 cm^{-1} bands mentioned by H and W (3) and the bands at 5804 and 5695 cm^{-1} cited by G and E (2). The frequencies we have observed correspond more closely to the 5780 and 5656 cm^{-1} frequencies given by G and E (2) for the polyethylene chain. They have been given the assignment $2\nu_a$ and $2\nu_s$ of the $-CH_2-$ vibrations respectively. The behavior of these bands when nylon is treated with HCl is similar to that mentioned for the other bands involving $-CH_2-$ modes. The 5150 cm^{-1} band is generally attributed to water and shows no dichroism.

Another band at 4960 cm^{-1} shows some σ dichroism and is no doubt that given at 4975 cm^{-1} by G and E (2) and assumed by them to be the third harmonic of a C=O vibration at 1640 cm^{-1}. However, Fraser (1) has assigned this band to a combination of the NH

vibration at 3300 cm^{-1} with the C=O vibration. The complete disappearance of this band in nylon treated with HCl favors the latter explanation since our earlier work (5) has shown that the effect of the HCl is much more pronounced on the 3300 cm^{-1} vibration than on the 1640 cm^{-1} vibration.

The band showing the greatest degree of dichroism is that at 4880 cm^{-1}. The parallel (π) dichroism agrees with that given by H and W (3) at 4850 cm^{-1}. There is agreement on the assignment of this band as a combination of the NH vibration at 3300 cm^{-1} and the amide II or NH deformation band at 1545 cm^{-1}. The band is absent in the spectrum of the HCl-treated samples, as expected, but it reappears when the HCl is removed, but with no dichroism (Fig. 5) or little dichroism (Fig. 4, for reason previously discussed).

Another absorption band showing π dichroism is found with a frequency of 4680 cm^{-1}. G and E (2) mention a band with low dichroism at a frequency of 4700 cm^{-1}. Fraser (1) gives it the assignment $2\nu_2+\nu_6$ or twice the NH deformation vibration of 690 cm^{-1} plus the NH stretching vibration of 3300 cm^{-1}. The association of this band with the NH group results in its disappearance when nylon is treated with HCl but it does not reappear when the HCl is removed.

A band at 4580 cm^{-1} shows little, if any, dichroism. H and W (3) mention a band at 4590 cm^{-1} as having σ dichroism. Fraser (1) cites this band as having a low dichroism and assigns to it the combination of the NH vibration at 3300 cm^{-1} with the amide III band at 1250 cm^{-1}. In the treated sample this band is just discernible as a shoulder on the broad absorption band covering the 5400–4500 cm^{-1} region. In the evacuated samples it is more pronounced. In the untreated sample, this band is accompanied by a band at 4550 cm^{-1} appearing as a small shoulder on the perpendicular spectrum only and possessing therefore some σ dichroism. Fraser (1) has calculated a band at 4490 cm^{-1} (10 cm^{-1} less than the 4500 cm^{-1} calculated for the 4590 cm^{-1} band) from a combination of twice the 1650 cm^{-1} C=O vibration with the 1280 cm^{-1} NH deformation mode. This might well be the band we observed at 4550 cm^{-1}. In the treated and evacuated samples a broad shoulder probably covers both 4580 and 4550 cm^{-1} bands.

The bands at 4350, 4275, 4230, and 4070 cm^{-1} are all combinations involving the asymmetric or symmetric CH_2 stretching vibrations plus one of the deformation modes. In the treated samples, the large degree of scattering obscures these bands, which, as a result, appear to have a much reduced intensity.

One peculiar feature of these bands is the difference between the parallel and the perpendicular vibrations in the 4220–4280 cm^{-1} region (Figs. 1 and 2). Whereas the 4275 cm^{-1} band is well separated from the 4230 cm^{-1} band in the perpendicular spectrum, the 4230 cm^{-1} band is displaced to a higher frequency, $\sim$4240 cm^{-1}, in the parallel spectrum, and appears to have some π dichroism. Fraser (1) mentions a band with a frequency of 4260 cm^{-1}, which is probably the same as our 4275 cm^{-1} band, and one at 4220 cm^{-1} with π dichroism. G and E (2) give bands at 4257, 4219, and 4202 cm^{-1}. The 4220 cm^{-1} appears as a shoulder in Fig. 2.

A small band at 3900 cm^{-1} with definite π dichroism has not been mentioned by other workers. It is not discernible in the samples treated with HCl. It could be a combination of the NH 3300 cm^{-1} band plus the 690 cm^{-1} deformation mode.

It is evident from these observations that any combination band involving the NH or peptide linkage is affected by the treatment of nylon with HCl whereas any change in the vibrations depending solely on the —CH_2— groups is only of a secondary nature. It is also clear that the HCl treatment results in a loss of orientation of the polymer chains. This is in accord with the conclusions drawn from our previous work in the

region of lower frequencies (5). If one accepts these conclusions a priori, then the results of these experiments can be regarded as confirmation for some of the assignments made in the overtone region of the nylon spectrum.

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THE SYNTHESIS OF ACETAMIDO-DEOXY KETOSES BY ACETOBACTER SUBOXYDANS

PART II[1]

J. K. N. JONES, M. B. PERRY, AND J. C. TURNER

ABSTRACT

The microbiological oxidation of 1-deoxy-1-*N*-methylacetamido-D-glucitol and 2-acetamido-1,2-dideoxy-D-glucitol yielded a syrupy ketose and a crystalline ketose respectively. Crystalline derivatives of each were prepared and structural investigations of the ketoses showed the former to be 6-deoxy-6-*N*-methylacetamido-L-xylohexulose and the latter to be 5-acetamido-5,6-dideoxy-L-xylohexulose.

INTRODUCTION

The microbiological oxidation of unsubstituted polyhydric alcohols has been studied extensively (1, 2, 3, 4, 5, 6), and the oxidation of terminal-substituted polyhydric alcohols has also been investigated in several laboratories (7, 8, 9, 10). Recently we reported the oxidation of the substituted hexitol 2-acetamido-2-deoxy-D-glucitol by *Acetobacter suboxydans* to 5-acetamido-5-deoxy-L-xylohexulose (11) and in this paper we wish to report the microbiological oxidation of 1-deoxy-1-*N*-methylacetamido-D-glucitol (I) to 6-deoxy-6-*N*-methylacetamido-L-xylohexulose (II), and of 2-acetamido-1,2-dideoxy-D-glucitol (III) to 5-acetamido-5,6-dideoxy-L-xylohexulose (IV).

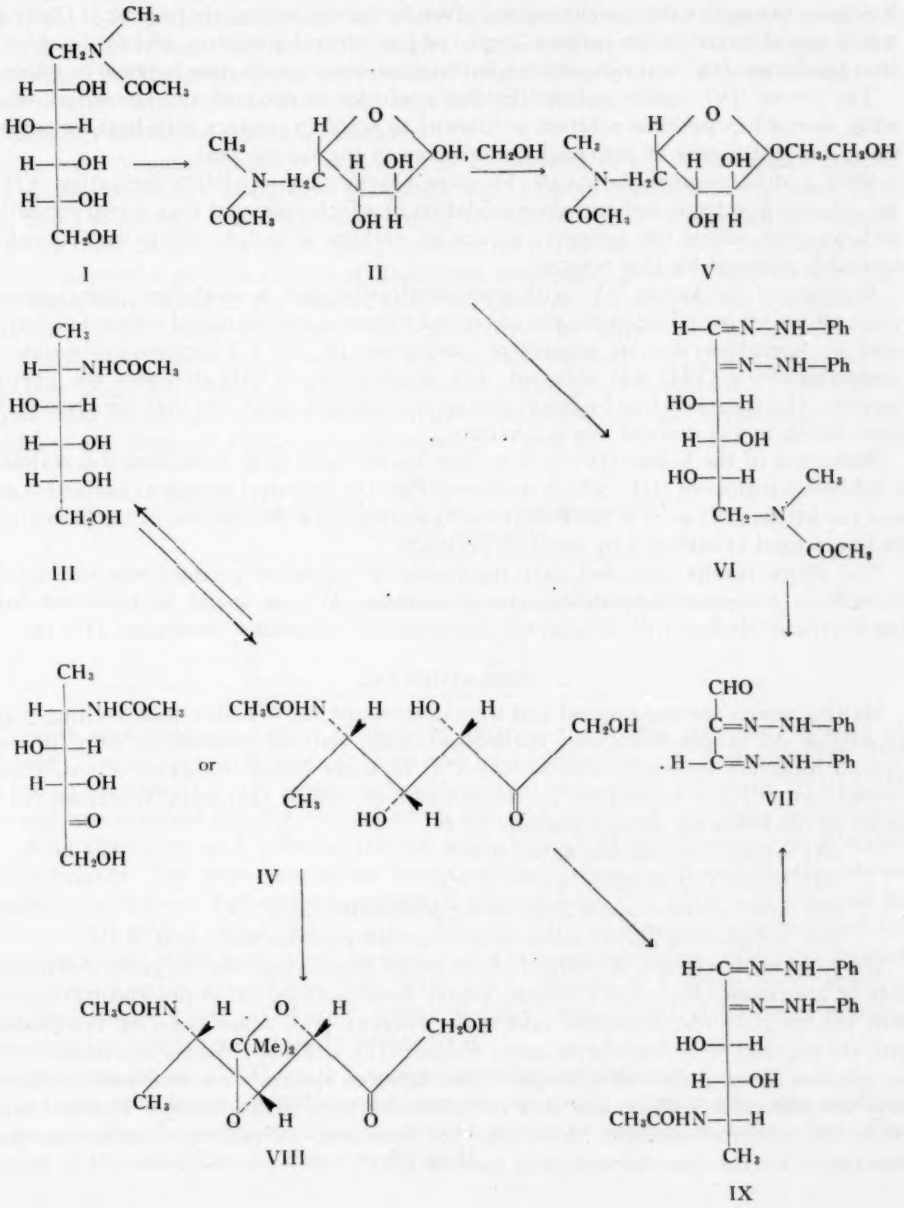
The oxidation of 1-deoxy-1-*N*-methylacetamido-D-glucitol (I) yielded a syrup which gave absorptions in the infrared corresponding to OH, CH, and C=O of the tertiary amide group. A weak band at 1730 cm^{-1} was also observed and was probably due to the presence of a small amount ($\sim$5%) of the acyclic form of the ketose. The results of periodate oxidation indicated that the main bulk of the material existed in the furanose ring form (II). Further evidence for a furanose ring form was given by the ready and rapid formation of a crystalline methyl glycoside (V) which was stable towards alkali but which was readily hydrolyzed with dilute acid. The rate of periodate oxidation of the glycoside (V) indicated that the two free hydroxyl groups, between which cleavage had occurred, were held in the trans configuration by the near-planar furanose ring.

The ketose (II) gave a crystalline phenylosazone (VI) which, when oxidized with periodate by the method of Hough, Powell, and Woods (12), consumed 2 moles of periodate, releasing 0.58 mole formic acid and no formaldehyde. The apparent low formic acid release agreed with the findings of Hough, Powell, and Woods, who obtained similar results from the periodate oxidation of monosaccharide and disaccharide phenylosazones (12). An immediate precipitate of the 1,2-bisphenylhydrazone of mesoxalaldehyde (VII) was obtained from the oxidation. The oxidation results indicated that the osazone (VI) possessed free hydroxyl groups at carbons 3, 4, and 5, and that the ketose (II) from which it was derived was a 2-ketose.

The ketose (II) was very slowly reduced by sodium borohydride to give a syrup which could not be crystallized. This product apparently consisted of the two expected isomeric hexitols although they could not be separated by paper chromatography in several solvent systems.

[1]*Manuscript received June 7, 1961.*
Contribution from the Department of Organic Chemistry, Queen's University, Kingston, Ontario.

The above results showed that the ketose had the indicated structure (II), the major portion being in the furanose ring form, and that the site of biological oxidation in 1-deoxy-1-*N*-methylacetamido-D-glucitol was at carbon 5, in accordance with the well-known enzyme specificity for oxidations at pH 5–6.5.



The oxidation of 2-acetamido-1,2-dideoxy-D-glucitol (III) by *Acetobacter suboxydans* gave crystalline 5-acetamido-5,6-dideoxy-L-xylohexulose (IV). The results of periodate oxidation indicated that enzymic oxidation had not occurred at the primary alcohol group of the hexitol. The formation of aldofuranose rings was thus excluded on this evidence and the ketose therefore probably existed in the acyclic zigzag form (IV). Evidence to support this conclusion was given by (*a*) the strong, sharp peak at 1735 cm^{-1} which was observed in the carbonyl region of the infrared spectrum, and (*b*) by the fact that the ketose (IV) was not oxidized by bromine water or alkaline hypoiodite solution.

The ketose (IV) rapidly reduced Fehling's solution in the cold and epimerized easily when warmed in pyridine solution or allowed to stand in contact with base for a short time, due to the ease of keto-enol tautomerism in the acyclic form.

With acidified acetone the ketose (IV) gave a syrupy isopropylidene derivative (VIII), the infrared spectrum and periodate oxidation of which indicated that acetal formation had occurred across the hydroxyl groups on carbons 3 and 4, which were therefore favorably situated for this reaction.

Reaction of the ketose (IV) with phenylhydrazine gave a crystalline phenylosazone (IX), which, on periodate oxidation, consumed 1 mole of periodate and released no formic acid or formaldehyde. An immediate precipitate of the 1,2-bisphenylhydrazone of mesoxalaldehyde (VII) was obtained. The above evidence indicated that the phenylosazone (IX) possessed free hydroxyl groups on carbons 3 and 4 and that the ketose (IV) from which it was derived was a 2-ketose.

Reduction of the ketose (IV) with sodium borohydride gave crystalline 2-acetamido-1,2-dideoxy-D-glucitol (III), which confirmed that the hydroxyl groups at carbons 3 and 4 of the ketose (IV) were in the D-*threo* configuration since the position of the keto group had been fixed at carbon 2 by previous evidence.

The above results indicated that the biological oxidation product was the acyclic 2-hexulose, 5-acetamido-5,6-dideoxy-L-xylohexulose (IV), as would be predicted from the Bertrand–Hudson rule for enzymic oxidation by *Acetobacter suboxydans* (13, 14).

EXPERIMENTAL

Melting points are uncorrected and were determined on a Fisher-John melting point apparatus. All evaporations were carried out under reduced pressure at 50° C or less. Optical rotations were measured at 23±3° C in water unless otherwise stated. Paper chromatography was carried out by the descending method (15) using Whatman No. 1 paper in the following solvent systems (v/v):

(A) butan-1-ol/ethanol/water, 9:3:3;
(B) butan-1-ol/pyridine/water, 5:3:2;
(C) ethyl acetate/acetic acid/formic acid/water, 18:3:1:4;
(D) 2-butanone/glacial acetic acid/saturated aqueous boric acid, 9:1:1.

The rates of movement of compounds on paper chromatograms are given relative to that of rhamnose (R_{rh} value). Ketose sugars were detected on paper chromatograms with the orcinol – trichloroacetic acid spray reagent (16), other reducing compounds with the *p*-anisidine hydrochloride spray reagent (17), and non-reducing compounds with the alkaline silver nitrate spray reagent (18). Infrared spectra were measured in chloroform solution or as a dispersion in a potassium bromide pellet, using a Perkin–Elmer Model 21 spectrophotometer. Formaldehyde produced in periodate oxidations was determined by the chromotropic acid method (19).

SECTION A. STUDIES ON 6-DEOXY-6-*N*-METHYLACETAMIDO-L-XYLOHEXULOSE

Preparation of 1-Deoxy-1-N-methylacetamido-D-glucitol

1-Deoxy-1-*N*-methylamino-D-glucitol (Aldrich Chem. Co. sample) was twice recrystallized from ethanol containing a little water to give a creamy-white product which had m.p. 128–129° C, $[\alpha]_D$ −14° (lit. values, m.p. 126° C, $[\alpha]_D$ −18.5±1° (20)).

1-Deoxy-1-*N*-methylamino-D-glucitol was *N*-acetylated in aqueous solution, using the method of Levvy and McAllan (21), to give a yellow syrup which slowly crystallized on desiccation. The product was recrystallized from methanol/ether, then from ethanol/ether to give white crystals which had m.p. 119–121° C, $[\alpha]_D$ −22°.

6-Deoxy-6-N-methylacetamido-L-xylohexulose

1-Deoxy-1-*N*-methylacetamido-D-glucitol (7 g), sorbitol (3 g), yeast extract powder (0.5 g), and potassium dihydrogen phosphate (0.05 g) were dissolved in tap water (140 ml), and the solution was distributed among six 250-ml conical flasks and autoclaved at 15 p.s.i. for 20 minutes. After being cooled, the sterile broths were inoculated with several drops of a 48-hour culture of *Acetobacter suboxydans* grown in sorbitol solution. The flasks were stored in the dark at room temperature and samples were removed at intervals, under sterile conditions, for examination by paper chromatography and estimation of copper-reducing value by the Somogyi method (22). The appearance of L-sorbose (R_{rh} 0.52, solvent A) was noted, and of a spot (R_{rh} 1.1, solvent A) which gave a pink color changing to green with the orcinol – trichloroacetic acid spray reagent. The results of the Somogyi estimations are shown in Table I.

TABLE I

Oxidation of 1-deoxy-1-*N*-methylacetamido-D-glucitol by *Acetobacter suboxydans*

Time (days)	% yield of ketose (corrected for the presence of L-sorbose)
6	7.2
12	23.6
19	35.6

Growth was terminated after 22 days by pouring the broths into two volumes of ethanol. The solution was filtered, deionized by passage through Amberlite I.R. 120 (H^+) and Duolite A4 (OH') resins, and concentrated to a syrup. L-Sorbose crystallized out and was removed and the residual syrup was then separated into three components by chromatography on a cellulose column using butan-1-ol half-saturated with water as the irrigant. The three components were L-sorbose, 1-deoxy-1-*N*-methylacetamido-D-glucitol, and 6-deoxy-6-*N*-methylacetamido-L-xylohexulose. The latter was obtained as a clear, light yellow syrup (2.2 g), $[\alpha]_D$ −57°. An infrared spectrum was obtained by smearing a little of the syrup onto the surface of a potassium bromide pellet, and showed the following main absorptions: OH (3410 cm^{-1}, strong), CH (2960 cm^{-1}, strong), saturated ketone C=O (1730 cm^{-1}, weak), tertiary amide C=O (1625 cm^{-1}, strong). The complete spectrum is given in Appendix A.

Periodate Oxidation of 6-Deoxy-6-N-methylacetamido-L-xylohexulose

An aqueous solution of 6-deoxy-6-*N*-methylacetamido-L-xylohexulose was oxidized under unbuffered conditions using a twofold excess of sodium metaperiodate. The results of the oxidation are shown in Table II.

TABLE II

Periodate oxidation of 6-deoxy-6-*N*-methylacetamido-L-xylohexulose

Time (hours)	Periodate uptake (moles/mole)	Formic acid (moles/mole)	Formaldehyde (moles/mole)
0.08	1.84	1.06	
0.17			0.05
1		1.11	
2			0.10
4	2.05	1.20	
4.5			0.23
6	2.14	1.26	
23			0.26
26	2.44	1.50	

Methyl 6-Deoxy-6-N-methylacetamido-L-xylohexulofuranoside

6-Deoxy-6-*N*-methylacetamido-L-xylohexulose (200 mg) was dissolved in anhydrous methanol (5 ml), and anhydrous methanolic hydrogen chloride (1%, 8 ml) added. The solution was allowed to stand at room temperature for 3½ hours, then neutralized with silver carbonate, filtered, and evaporated to dryness. The resulting pale yellow syrup gave a bright yellow spot on paper chromatograms (R_{rh} 1.57, solvent A) with the *p*-anisidine hydrochloride spray reagent. The syrup gave only a faint spot due to unreacted 6-deoxy-6-*N*-methylacetamido-L-xylohexulose with the alkaline silver nitrate spray reagent. After desiccation for 3 days the syrup crystallized and crystallization was speeded by the addition of methanol/ethyl acetate. The crystals were filtered off, dried, and recrystallized twice from methanol/ethyl acetate to give white needles (50 mg) which had m.p. 109–110° C, $[\alpha]_D$ −97°. The glycoside gave absorptions in the infrared corresponding to OH (3480 cm^{-1}), CH (2940, 2880 cm^{-1}), and tertiary amide C=O (1600 cm^{-1}). The complete spectrum is given in Appendix B. Anal. Calc. for $C_{10}H_{19}O_6N$: C, 48.2%; H, 7.6%; N, 5.6%. Found: C, 48.1%; H, 7.4%; N, 5.7%.

Periodate Oxidation of Methyl 6-Deoxy-6-N-methylacetamido-L-xylohexulofuranoside

The glycoside was oxidized with a twofold excess of sodium metaperiodate in unbuffered aqueous solution. The results of the oxidation are given in Table III. No formaldehyde was detected in the oxidation mixture.

TABLE III

Periodate oxidation of methyl 6-deoxy-6-*N*-methylacetamido-L-xylohexulofuranoside

Time (hours)	Periodate uptake (moles/mole)	Formic acid (moles/mole)
0.08	0.07	0.00
5	0.88	0.03
9	0.98	0.00
23.5	1.00	0.02

6-Deoxy-6-N-methylacetamido-L-xylohexulose Phenylosazone

The osazone was prepared by the usual method using freshly distilled phenylhydrazine and glacial acetic acid. It was recrystallized twice from ethanol/ethyl acetate and once from ethanol/ether to give a bright yellow powder, m.p. 182–183° C. The osazone gave absorptions in the infrared corresponding to OH (3430 cm^{-1}), NH (3270 cm^{-1}), aromatic

CH (3080 cm^{-1}), aliphatic CH (2940, 2880 cm^{-1}), tertiary amide C=O (1625 cm^{-1}), and the aromatic ring (1610, 1500, 750, 690 cm^{-1}). The complete spectrum is given in Appendix C. Anal. Calc. for $C_{21}H_{27}O_4N_5$: C, 61.0%; H, 6.5%; N, 16.9%. Found: C, 60.5%; H, 6.6%; N, 16.2%.

Periodate Oxidation of 6-Deoxy-6-N-methylacetamido-L-xylohexulose Phenylosazone

The osazone was oxidized in 50% aqueous ethanol by the method of Hough, Powell, and Woods (12). The results of the oxidation are shown in Table IV.

TABLE IV

Periodate oxidation of 6-deoxy-6-*N*-methylacetamido-L-xylohexulose phenylosazone

Time (hours)	Periodate uptake (moles/mole)	Formic acid (moles/mole)	Formaldehyde (moles/mole)
0.42	1.90	0.41	0.00
1.66	2.05	0.59	0.00
3.08	2.14	0.58	0.00

1,2-Bisphenylhydrazone of Mesoxalaldehyde (23)

In the periodate oxidation of 6-deoxy-6-*N*-methylacetamido-L-xylohexulose phenylosazone, a curdy mass of orange-yellow needles was precipitated 30 seconds after oxidation had started. The crystals of the 1,2-bisphenylhydrazone of mesoxalaldehyde were centrifuged off and the supernatant returned to the flask for oxidation studies. The crystals were washed with water, dried, and recrystallized from 50% aqueous ethanol, m.p. 189–191° C. An authentic specimen had m.p. 193–194° C and the mixed m.p. was 189–191° C. The infrared spectra of the authentic and derived specimens were identical over the range 4000–600 cm^{-1}. The spectra were given in a previous publication (11).

Sodium Borohydride Reduction of 6-Deoxy-6-N-methylacetamido-L-xylohexulose

An aqueous solution of 6-deoxy-6-*N*-methylacetamido-L-xylohexulose (100 mg) was reduced with an equal weight of sodium borohydride at 5° C for 18 hours. After removal of sodium borohydride and sodium borate the product was obtained as a syrup (100 mg) which gave two spots, R_{rh} 1.1 (unreduced ketose) and R_{rh} 0.61 (polyhydric alcohols) in solvent A, with the alkaline silver nitrate spray reagent. The polyhydric alcohols were separated from the ketose on Whatman 3 MM paper and obtained as a syrup (75 mg) which gave one spot with the alkaline silver nitrate spray reagent on chromatography in solvents A, B, C, and D. The syrup gave one fraction only, when passed through a column of Dowex 50 W resin (8% cross-linked with divinylbenzene, barium salt form, 200–400 mesh).

The syrup had $[\alpha]_D$ −17° ($[\alpha]_D$ of 1-deoxy-1-*N*-methylacetamido-D-glucitol was −22°) and it was concluded that it contained 1-deoxy-1-*N*-methylacetamido-D-glucitol and probably the isomeric L-iditol derivative. Certainly some 1-deoxy-1-*N*-methylacetamido-D-glucitol was present since oxidation of the syrupy mixture by *Acetobacter suboxydans* gave some 6-deoxy-6-*N*-methylacetamido-L-xylohexulose.

Section B. Studies on 5-Acetamido-5,6-dideoxy-L-xylohexulose

Preparation of 2-Acetamido-1,2-dideoxy-D-glucitol

2-Amino-2-deoxy-D-glucose Diethyl Dithioacetal

2-Amino-2-deoxy-D-glucose hydrochloride (15 g), fuming hydrochloric acid (120 ml), and ethanethiol (45 ml) were shaken in a pressure bottle at room temperature for 20 hours.

The solution was diluted with ethanol, lead acetate was added, and then lead carbonate was added to neutrality. The solution was filtered and the lead salts were washed with ethanol. The filtrate and washings were combined and saturated with hydrogen sulphide, a little charcoal was added, and the solution was filtered and concentrated to a yellow syrup. The syrup was dissolved in water and passed through Duolite A4(OH′) resin. The eluate was concentrated to give crystalline 2-amino-2-deoxy-D-glucose diethyl dithioacetal (10.9 g), m.p. 107–109° C, $[\alpha]_D$ −22° (lit. values, m.p. 109–110° C, $[\alpha]_D$ −24° (24)).

*2-Amino-2-deoxy-*D*-glucose Diethyl Dithioacetal Penta-acetate*

2-Amino-2-deoxy-D-glucose diethyl dithioacetal (10 g) was acetylated with acetic anhydride in pyridine solution at room temperature for 24 hours to give 2-amino-2-deoxy-D-glucose diethyl dithioacetal penta-acetate as a colorless syrup (17 g), $[\alpha]_D$ +2° (*c*, 1.54 in chloroform) (lit. value $[\alpha]_D$ +1° (chloroform) (24)).

*2-Acetamido-1,2-dideoxy-*D*-glucitol*

2-Amino-2-deoxy-D-glucose diethyl dithioacetal penta-acetate (17 g) was reductively desulphurized by being boiled under reflux with Raney nickel catalyst for 5 hours in ethanol solution. The solution was filtered and the catalyst was washed several times with hot ethanol. The filtrate and washings were combined and evaporated to dryness, giving 2-amino-1,2-dideoxy-D-glucitol penta-acetate as a semicrystalline syrup (8.6 g). The syrup was dissolved in methanol (400 ml) and cooled to 0° C. A stream of anhydrous ammonia was passed into the solution for 20 minutes and the solution allowed to stand for 2 hours at room temperature, then evaporated to dryness. The crystalline residue was dissolved in methanol and an equal volume of chloroform was added, followed by ether to incipient opalescence. Small needles of 2-acetamido-1,2-dideoxy-D-glucitol crystallized out and were recrystallized by the same method to give a chromatographically pure product (3.9 g) which had m.p. 160–162° C, $[\alpha]_D$ −14° (lit. values, m.p. 162–164° C, $[\alpha]_D$ −9° (25)).

*5-Acetamido-5,6-dideoxy-*L*-xylohexulose*

2-Acetamido-1,2-dideoxy-D-glucitol (3 g), sorbitol (3 g), yeast extract powder (0.5 g), and potassium dihydrogen phosphate (0.05 g) were dissolved in tap water (100 ml). The solution was distributed among five 250-ml conical flasks and autoclaved at 15 p.s.i. for 30 minutes. After being cooled to room temperature, the broths were inoculated with several drops of a 48-hour culture of *Acetobacter suboxydans* grown in sorbitol solution, and stored in the dark at room temperature. Samples were removed at intervals under sterile conditions for chromatographic examination and estimation of copper-reducing values by the Somogyi method (23).

The appearance of L-sorbose (R_{rh} 0.49, solvent A), and a spot (R_{rh} 1.13, solvent A) which gave a yellow color with the orcinol – trichloroacetic acid spray reagent was noted. The results of the Somogyi estimations showed a 16.7% yield of 5-acetamido-5,6-dideoxy-L-xylohexulose after 7 days and a 69% yield after 20 days. Growth was terminated after 31 days by pouring the broths into 2 volumes of ethanol. The solution was filtered and rapidly passed through small beds of Amberlite I.R. 120 (H^+) and Duolite A4 (OH′) resins at 5° C. The eluate and washings were concentrated at 35–40° C to a brown syrup which slowly crystallized on the addition of ethanol. The crystalline L-sorbose was removed and the residual syrup was fractionated on a cellulose column using butan-1-ol half-saturated with water as the irrigant. Three fractions were obtained: 5-acetamido-5,6-dideoxy-L-xylohexulose, 2-acetamido-1,2-dideoxy-D-glucitol, and L-sorbose.

The 5-acetamido-5,6-dideoxy-L-xylohexulose was obtained as a clear brown syrup (2.1 g), $[\alpha]_D$ −38°. The syrup crystallized after several months but unfortunately only after all the structural work had been completed on the syrup. The crystals were recrystallized from ethanol/ether as rosettes of needles (15 mg) and due to the small amount, a completely pure specimen could not be obtained. The crystals had m.p. 91–93° C, $[\alpha]_D$ −40°.

Anal. Calc. for $C_8H_{15}O_5N$: C, 46.8%; H, 7.3%; N, 6.8%. Found: C, 46.0%; H, 7.2%; N, 6.7%.

The crystals gave absorptions in the infrared corresponding to OH (3400 cm^{-1}), NH (3280 cm^{-1}), CH (2960, 2900 cm^{-1}), saturated ketone C=O (1735 cm^{-1}), amide I (1645 cm^{-1}), amide II (1575 cm^{-1}). The complete spectrum is given in Appendix D.

5-Acetamido-5,6-dideoxy-L-xylohexulose rapidly reduced Fehling's solution in the cold. It was not affected by bromine water at room temperature for 3 hours since no other spots could be detected on paper chromatograms run in solvent A, after bromine water treatment.

Periodate Oxidation of 5-Acetamido-5,6-dideoxy-L-xylohexulose

The ketose was oxidized with sodium metaperiodate at pH 7.5, and under unbuffered conditions and the liberated formaldehyde determined. The results are shown in Table V.

TABLE V

Formaldehyde estimations in the periodate oxidation of 5-acetamido-5,6-dideoxy-L-xylohexulose

	Formaldehyde (moles/mole)	
Time (hours)	pH 7.5	pH 3–4 (unbuffered)
0.17	0.97	0.43
1.17		0.43
4.4		0.41
5	0.89	
9.7		0.39
19	0.76	

Alkaline Hypoiodite Oxidation of 5-Acetamido-5,6-dideoxy-L-xylohexulose

5-Acetamido-5,6-dideoxy-L-xylohexulose was oxidized with alkaline hypoiodite solution by the standard method (26). The results indicated that the 5-acetamido-5,6-dideoxy-L-xylohexulose contained 10% aldose. However, it was found that the pH 11.4 buffer used in the oxidation caused epimerization of the ketose to aldoses which were detected as two new spots on paper chromatograms, R_{rh} 1.6 and R_{rh} 1.8 in solvent A, with the alkaline silver nitrate and *p*-anisidine hydrochloride spray reagents. A similar pattern of spots was obtained when 5-acetamido-5,6-dideoxy-L-xylohexulose was heated at 100° C for 3 hours in pyridine solution. From these results it was concluded that the value of 10% aldose content resulted from epimerization and that the 5-acetamido-5,6-dideoxy-L-xylohexulose contained very little, if any, aldose.

5-Acetamido-5,6-dideoxy-3,4-O-isopropylidene-L-xylohexulose

5-Acetamido-5,6-dideoxy-L-xylohexulose (200 mg) was dissolved in acetone (100 ml) containing concentrated sulphuric acid (4 drops) and shaken for 24 hours at room temperature. The solution was neutralized with barium carbonate, filtered, and evaporated to dryness and the resulting syrup was examined on paper chromatograms run in

solvent A. Two spots were observed with the alkaline silver nitrate spray, R_{rh} 1.2 (5-acetamido-5,6-dideoxy-L-xylohexulose) and R_{rh} 2.5 (5-acetamido-5,6-dideoxy-3,4-*O*-isopropylidene-L-xylohexulose). The isopropylidene derivative was separated by chromatography in solvent A on Whatman 3 MM paper and obtained as a syrup (74 mg), $[\alpha]_D$ −19° (*c*, 1.16 in ethanol). The syrup rapidly reduced Fehling's solution in the cold and gave absorptions in the infrared corresponding to OH (3500 cm^{-1}), CH (3010, 2980, 2910 cm^{-1}), saturated ketone C=O (1730 cm^{-1}), amide I (1670 cm^{-1}), and amide II (1525 cm^{-1}). The complete spectrum is given in Appendix E.

Periodate Oxidation of 5-Acetamido-5,6-dideoxy-3,4-O-isopropylidene-L-xylohexulose

The isopropylidene ketose was oxidized with a twofold excess of sodium metaperiodate in 50% aqueous ethanol and the liberated formaldehyde determined. The results are shown in Table VI.

TABLE VI

Periodate oxidation of 5-acetamido-5,6-dideoxy-3,4-*O*-isopropylidene-L-xylohexulose

Time (hours)	Formaldehyde (moles/mole)
0.17	0.07
1.17	0.27
4.4	0.29
9.7	0.31

5-Acetamido-5,6-dideoxy-L-xylohexulose Phenylosazone

5-Acetamido-5,6-dideoxy-L-xylohexulose (200 mg) was treated with freshly distilled phenylhydrazine and glacial acetic acid by the usual method to give a fine yellow powder (110 mg). The osazone was recrystallized from ethanol and had m.p. 156–158° C (decomposes). It gave absorptions in the infrared corresponding to OH (3460 cm^{-1}), NH (3370 cm^{-1}), aromatic CH (3080 cm^{-1}), aliphatic CH (3000, 2910, 2860 cm^{-1}), amide I (1655 cm^{-1}), amide II (1560 cm^{-1}), and the aromatic ring (1610, 1500, 745, 690 cm^{-1}). The complete spectrum is given in Appendix F. Anal. Calc. for $C_{20}H_{25}O_3N_5$: C, 62.7%; H, 6.5%; N, 18.3%. Found: C, 62.85%; H, 6.6%; N, 18.1%.

Periodate Oxidation of 5-Acetamido-5,6-dideoxy-L-xylohexulose Phenylosazone

The osazone was oxidized with sodium metaperiodate in 50% aqueous ethanol using the method of Hough, Powell, and Woods (12). The results of the oxidation are shown in Table VII.

TABLE VII

Periodate oxidation of 5-acetamido-5,6-dideoxy-L-xylohexulose phenylosazone

Time (hours)	Periodate uptake (moles/mole)
0.42	1.02
1.75	0.98
4.0	1.07

No formic acid or formaldehyde were detected in the oxidation mixture.

During the oxidation a bright orange-yellow precipitate of the 1,2-bisphenylhydrazone of mesoxalaldehyde (23) was obtained. Its identity was proved by melting point, mixed melting point, and identical infrared spectrum with an authentic specimen as described previously in Section A of this publication.

Sodium Borohydride Reduction of 5-Acetamido-5,6-dideoxy-L-xylohexulose

5-Acetamido-5,6-dideoxy-L-xylohexulose (115 mg) was reduced in aqueous solution with an equal weight of sodium borohydride at 0° C for 3 hours. Excess sodium borohydride was converted to sodium borate which was removed as methyl borate after passage through Amberlite I.R. 120 (H^+) resin. The product was obtained as a clear colorless syrup (90 mg). The syrup was dissolved in methanol, an equal volume of chloroform was added, then ether to incipient opalescence, and the solution was stored at 0° C. The resulting crystals were filtered off, washed with methanol/ether, and dried (21 mg). A second crop of crystals could not be obtained from the mother liquors. The crystals had m.p. 163–164° C and an authentic specimen of 2-acetamido-1,2-dideoxy-D-glucitol had m.p. 160–162° C. The mixed m.p. was 157–159° C. The crystals (and mother liquors) gave one spot on paper chromatograms with the alkaline silver nitrate spray reagent. The infrared spectra of the crystals and the authentic specimen of 2-acetamido-1,2-dideoxy-D-glucitol were identical over the range 4000–600 cm^{-1}. The crystals had $[\alpha]_D$ −16° and the authentic material had $[\alpha]_D$ −14°.

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APPENDIX

Infrared Spectra

The following abbreviations are used: S = strong, M = medium, W = weak; wave numbers are expressed in cm^{-1}.

(A) 6-Deoxy-6-N-methylacetamido-L-xylohexulose (smeared on surface of KBr pellet) 3410 (S), 2960 (S), 1730 (W), 1625 (S), 1505 (S), 1425 (S), 1375 (M), 1295 (M), 1255 (M), 1135 (M), 1075 (S), 1035 (S), 935 (M), 895 (W), 865 (W), 815 (W), 695 (W).

*(B) Methyl 6-Deoxy-6-N-methylacetamido-*L*-xylohexulofuranoside* (0.8% in KBr)
3400 (S), 2940 (M), 2880 (M), 1600 (S), 1505 (M), 1465 (M), 1435 (S), 1415 (M), 1385 (M), 1340 (M), 1320 (M), 1280 (M), 1245 (M), 1215 (M), 1165 (S), 1135 (M), 1100 (S), 1050 (M), 1025 (S), 985 (M), 935 (M), 890 (M), 845 (M), 805 (M), 780 (W), 700 (M), 670 (M).

*(C) 6-Deoxy-6-N-methylacetamido-*L*-xylohexulose Phenylosazone* (0.8% in KBr)
3430 (S), 3270 (S), 3080 (S), 2940 (M), 2880 (M), 1625 (S), 1610 (S), 1590 (S), 1540 (S), 1515 (S), 1500 (S), 1460 (M), 1425 (S), 1380 (S), 1340 (M), 1315 (S), 1290 (S), 1260 (S), 1175 (S), 1150 (M), 1105 (S), 1060 (S), 1010 (S), 965 (M), 900 (M), 880 (M), 845 (M), 825 (W), 795 (M), 775 (W), 750 (S), 725 (M), 690 (S).

*(D) 5-Acetamido-5,6-dideoxy-*L*-xylohexulose* (0.8% in KBr)
3400 (S), 3280 (S), 3100 (S), 2960 (M), 2900 (M), 1735 (S), 1645 (S), 1575 (S), 1460 (M), 1430 (M), 1385 (M), 1340 (M), 1325 (M), 1285 (M), 1240 (M), 1185 (W), 1155 (W), 1135 (W), 1115 (S), 1100 (S), 1080 (M), 1050 (M), 975 (W), 965 (W), 955 (W), 850 (W), 825 (W), 740 (M), 690 (M), 655 (M).

*(E) 5-Acetamido-5,6-dideoxy-3,4-O-isopropylidene-*L*-xylohexulose* (6% in chloroform)
3500 (W), 3400 (W), 3010 (M), 2980 (W), 2910 (W), 2410 (W), 1730 (M), 1670 (S), 1525 (S), 1460 (M), 1395 (S), 1385 (S), 1335 (M), 1240 (S), 1170 (M), 1085 (M), 1065 (M), 1045 (M), 1015 (M), 930 (W), 875 (M), 795 (M), 720 (M), 660 (W).

*(F) 5-Acetamido-5,6-dideoxy-*L*-xylohexulose Phenylosazone* (0.8% in KBr)
3460 (S), 3370 (S), 3290 (S), 3080 (M), 3000 (M), 2910 (M), 2860 (W), 1935 (W), 1655 (S), 1610 (S), 1585 (S), 1560 (S), 1540 (S), 1520 (S), 1505 (S), 1460 (S), 1427 (S), 1385 (S), 1307 (S), 1290 (S), 1260 (S), 1175 (M), 1160 (M), 1120 (M), 1080 (M), 1045 (S), 1030 (M), 1015 (M), 975 (W), 940 (W), 905 (W), 870 (W), 845 (W), 815 (W), 785 (M), 755 (S), 745 (S), 690 (S).

THE DIFFUSION OF "ATTACHED" INERT-GAS ACTIVITY[1]

ROGER KELLY

ABSTRACT

It was shown previously that, when an inert gas is irradiated with neutrons in the presence of a powdered solid, between 0.1 and 14% of the induced inert-gas activity is firmly "attached" to the solid. The manner in which attached inert-gas activity is released at temperatures between 50 and 800° C has now been studied. Release data were assembled for a number of systems, and it was noted that the release was reproducible and apparently a diffusion phenomenon. Several theoretical treatments based on diffusion theory were then explored. Agreement between theory and observation was poor if a constant activation enthalpy was assumed. Agreement was good, on the other hand, with theory that took account of the damaged condition of the solid, and the existence of composition anomalies, in the surface region where the inert-gas activity was attached. The damage and composition anomalies were assumed to lead to a spectrum of activation enthalpies and thence to a simplified diffusive motion involving a single rate-controlling jump. The activation-enthalpy spectra for the systems Ar–Nb and Xe–Nb were found to be identical, extending from about 25 to 47 kcal. The spectrum for Xe–Nb_2O_5 extended from about 28 to 76 kcal, and was, in general, similar to the spectra for Xe–SiO_2, Ar–TiO_2, and Xe–TiO_2.

In a recent paper (1), experiments were described in which the inert gases argon, krypton, and xenon were irradiated with neutrons in the presence of various powders. It was found that the major portion of the induced inert-gas activity could be pumped off the powders at room temperature, though the last 0.1 to 14% (depending on the gas and powder used) was not released till the powders were heated. The latter activity was said to be "attached", and the ratio of attached to total activity was called the "attachment efficiency" (*A*). A temperature of about 800° C was necessary for a complete release of attached activity.

The present work concerns the manner in which attached inert-gas activity is released at temperatures below 800° C, in other words, in the temperature region where the extent of release is noticeably dependent on time and temperature. Release data are given for several combinations of inert gas and powder (or other solid). It is noted that the release is reproducible, and apparently a diffusion phenomenon. Several theoretical treatments based on diffusion theory are then examined for consistency with the experimental results. Finally, the concepts involved in the theoretical treatment that is most successful are discussed in connection with the over-all attachment process and in other respects.

EXPERIMENTAL

The apparatus and experimental techniques were similar to those described previously (1). A mixture of a powder (or other solid) and inert gas was sealed in a quartz capsule and irradiated overnight with neutrons at a flux of about 1×10^{13} neutrons cm^{-2} sec^{-1}. The capsule was then placed in a vacuum system (Fig. 1A of reference 1) and cracked open. That portion of the inert-gas activity remaining in the gas phase was pumped off, and, for the present purposes, need not be further considered. (The pumping had to be continued for 1½ to 3 hours before the evolution of activity ceased.) The remaining inert-gas activity was now slowly expelled by heating the solid, firstly to various temperatures in the region 50 to 800° C, and finally to 1000° C. (The heating at 1000° C ensured that the attached inert gas was completely released (cf. p. 665 of reference 1).)

[1]*Manuscript received August 16, 1961.*
Contribution from the Development Chemistry Branch, Atomic Energy of Canada Limited, Chalk River, Ontario.
Issued as A.E.C.L. No. 1362.

A trap containing charcoal at liquid-nitrogen temperature served to collect the released activity and to position it over a gamma-scintillation crystal (Fig. 1B of reference 1). Gamma counts were taken at intervals of 1 to 4 minutes, depending on the rate at which the activity was being released.

For some of the experiments, a trap containing charcoal at 300° C was introduced into the vacuum line ahead of the collecting trap. Charcoal, provided it is sufficiently hot, does not noticeably impede the movement of inert gases, though it will stop potential contaminants such as arsine or iodine. (For the behavior of *unheated* charcoal, see Fig. 3 of reference 1.)

The following solids were used:

Nb, Nb_2O_5, SiO_2, TiO_2 (commercial powders),
SiO_2 (quartz rods with 1-mm diameter),
TiO_2 (sintered balls in the size range from 20 to 60 mesh).[2]

To determine the importance of surface effects, each solid was studied both in an as-received condition, and also after ignition at 500 or 1000° C. The ignitions lasted ½ hour, with the first 10 minutes in air and the remaining 20 minutes in vacuum. Inert gas did not appear to attach to non-ignited quartz rods. This was probably due to the presence of a film of grease, for normal attachment took place with rods that had been washed with ether in a Soxhlet apparatus.

RESULTS

The results will be expressed in terms of the "fractional release" (F), which is defined as the fraction of the total attached inert-gas activity that has been released at a given stage of an experiment. Figs. 1A and 1B give typical curves for fractional release as a function of time. Note how, at a given temperature, activity at first came off rapidly, but its rate of release soon decreased, so that a comparatively level region (i.e. a "plateau") resulted. The plateau effect was less well developed with the niobium than with the other solids.

The initial release of inert-gas activity is seen from Figs. 1A and 1B to be so rapid that, at any given temperature, much of the activity was released in a time which was comparable to *each* of the following: (i) the time to bring the specimens up to temperature (2 to 3 minutes), (ii) the time taken by the activity to move through the vacuum system to the gamma counter (1 to 2 minutes), (iii) the duration of each gamma count (1 minute). As a result, the activities measured during the first 5 to 10 minutes that a specimen was held at a given temperature were probably low, and curves of F-versus-time would be difficult to analyze theoretically.

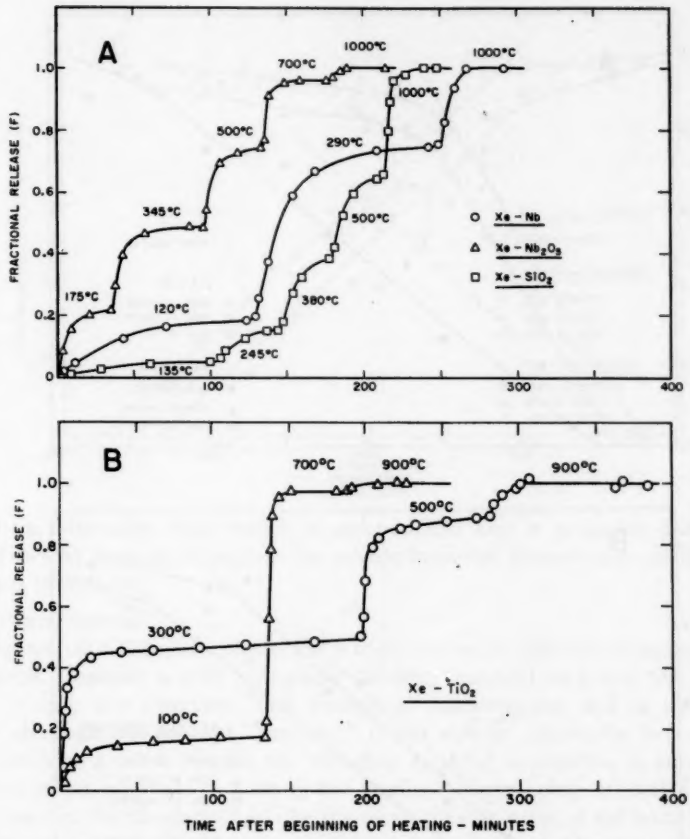
An alternative way of treating the data, which avoids the effect just described, is to plot fractional release after a fairly long time (e.g. 30 minutes) against temperature: Figs. 2A, 2B, and 2C. A number of conclusions can be drawn from Figs. 2A, 2B, and 2C.

(i) The release phenomenon is reproducible.

(ii) In general, release proceeds linearly over a wide range of temperature. There is a slight deviation from linearity at high temperatures with the oxides, and a much greater deviation with niobium, though the exceptional behavior of niobium is possibly due to the fact that part of the niobium surface is sufficiently oxidized to behave as Nb_2O_5.

(iii) In the two cases where argon and xenon are both used with a given solid (Nb and TiO_2), indistinguishable release behavior is observed. If it is borne in mind that xenon adsorbs much more strongly than argon (2), this observation leads to the conclusion that

[2]*The* TiO_2 *balls were kindly contributed by Titanium Alloy Manufacturing Division, National Lead Co., Niagara Falls, N.Y.*



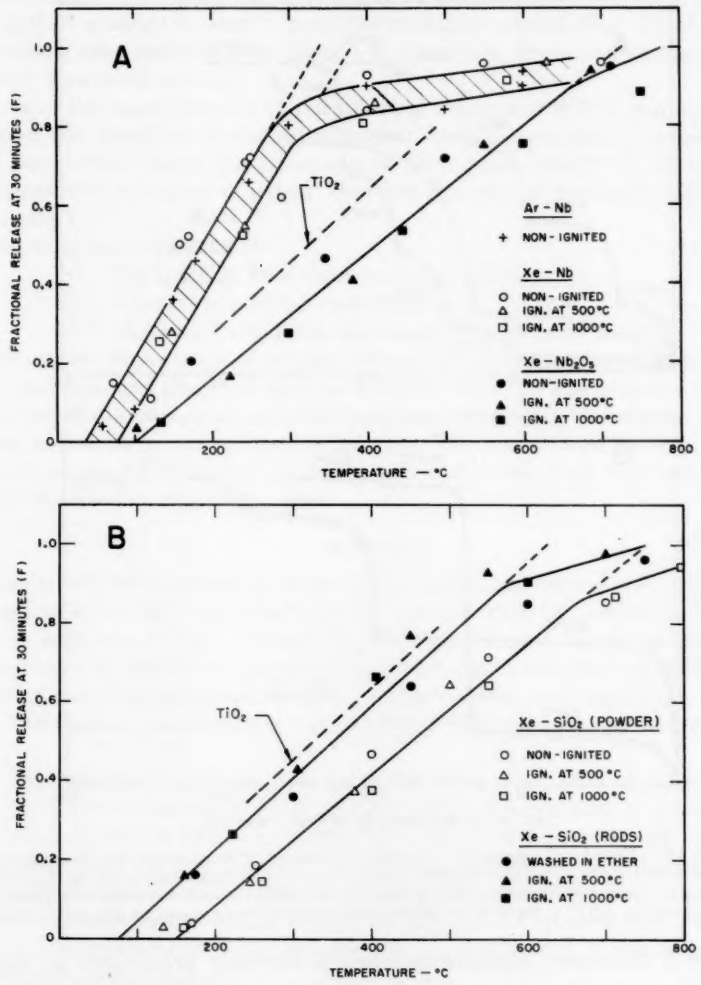
FIGS. 1A and 1B. Fractional release as a function of time for ^{125}Xe activity that has become attached to various solids following (n,γ) events. Selected points from typical experiments are shown for each solid. In each experiment the temperature was raised rapidly (i.e. within 2 to 3 minutes) to a given value, was held constant to within ±0.5° C for at least 30 minutes, and was then raised to the next value indicated.

release *is not* a desorption phenomenon, and is therefore presumably an example of diffusion.

(iv) Within the limits of the experimental scatter, there is no pronounced difference in the release behavior between solids in an as-received and ignited condition. This may be taken as evidence that release *is not* due to a recrystallization, sintering, or other alteration of the solid surface that might take place during an experiment. Once again release could be due to diffusion. (The release of I_2 from irradiated TeO_2 at elevated temperatures is an example where sintering is important (3).)

(v) The two forms of SiO_2 and TiO_2 give somewhat different results. Presumably the surface structures are different.

The main error associated with Figs. 2A, 2B, and 2C arises from the fact that each specimen was studied at a series of successively higher temperatures, yet the data at a given temperature were treated without regard to previous heatings. The justification for the procedure followed lies in the nature of the *F*-versus-time behavior: much of the activity ultimately released at a given temperature comes out in a few minutes; at a



FIGS. 2A, 2B, and 2C. Fractional release at 30 minutes as a function of temperature for ^{41}Ar and ^{129}Xe activities that have become attached to various solids. All results are shown. The curve for niobium is given a second dimension because the results are particularly scattered. The position of the curve for powdered TiO_2 is indicated in Figs. 2A and 2B for comparison.

higher temperature this same activity would therefore have come out in a time appreciably less than a few minutes, and the time scale at the higher temperature would be in error only to this extent.

DISCUSSION

(A) THEORETICAL

It has been shown that the release at elevated temperatures of inert-gas activity that has become attached to a solid is characterized by a plateau effect when F is plotted versus time, and by a wide temperature range when F (at 30 minutes) is plotted versus

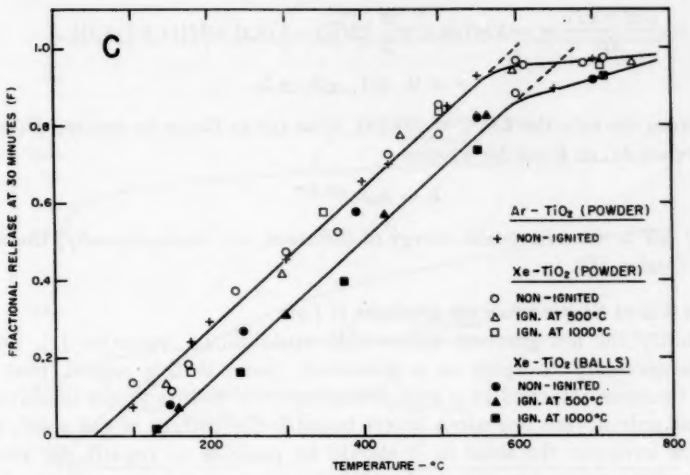


FIG. 2B.

temperature. Moreover, this release is reproducible and is probably due to diffusion. There follows an attempt to explain the release behavior theoretically using the concepts of diffusion theory.

General Considerations

The first step in a diffusion calculation is to decide on the differential equation governing the diffusion. Consider a solid containing diffusing material such that the concentration changes in only one direction. This change in concentration will be referred to as a *gradient*, although the concept "gradient" is not strictly applicable in a discontinuous medium such as a solid. Regard the diffusing material as residing in successive lattice planes located at intervals of λ along the gradient, there being $M(r\lambda,t)$ atoms per unit area at time t in the rth plane. Let τ be the mean time an atom of diffusing material stays in a given site (not *plane*) before jumping to a new site, and β be the probability that a jump will be into a new plane. Assume for the sake of simplicity that, for all jumps of significant probability, τ and β have the same values, while r changes by only 0 or 1 unit. The increment of $M(r\lambda,t)$ in time interval Δt, $\Delta t \ll \tau$, can then be written as follows (cf. references 4 and 5):

$$M(r\lambda,t+\Delta t) = \left(1-\frac{\Delta t}{\tau}\beta\right)M(r\lambda,t)+\frac{\Delta t}{\tau}\cdot\frac{\beta}{2}\{M[(r-1)\lambda,t]+M[(r+1)\lambda,t]\}$$

$$r = 0, \pm 1, \pm 2, \pm 3, \ldots .$$

This difference equation can be simplified in two ways. If $M(r\lambda,t)$ varies slowly with r, i.e. the gradient is always low, it yields the well-known partial-differential equation

$$[1] \qquad \frac{\partial M(x,t)}{\partial t} = \frac{k\lambda^2}{2}\cdot\frac{\partial^2 M(x,t)}{\partial x^2},$$

where $k \equiv \beta/\tau$ is the "diffusion rate constant", i.e. the rate at which diffusing material jumps along the gradient; $k\lambda^2/2 = \beta\lambda^2/2\tau$ is the "diffusion coefficient" (D); and x is the distance along the gradient. The quantity $r\lambda$ has been replaced with x to emphasize the fact that equation [1] is defined continuously in the space co-ordinate. If, on the other hand, no restrictions are placed on the gradient, a less complete reduction is obtained:

$$[2] \qquad \frac{dM(r\lambda,t)}{dt} = -kM(r\lambda,t)+\frac{k}{2}\{M[(r-1)\lambda,t]+M[(r+1)\lambda,t]\}$$

$$r = 0, \pm1, \pm2, \pm3, \ldots .$$

It follows from the relation $k\lambda^2/2 = D$ that, in so far as D can be written $D_0\exp(-\Delta H/RT)$ (cf. reference 4), so k can be written

$$[3] \qquad k = k_0 e^{-\Delta H/RT}.$$

The quantity ΔH is the activation *energy* of diffusion, or, more properly, the activation *enthalpy* of diffusion (6).

Diffusion of a Plane Source when the Gradient is Low

Consider firstly the low-gradient differential equation, i.e. equation [1]. To use this equation it is necessary to agree on a geometry. Note, in this regard, that inert-gas activity that becomes attached to a solid following (n,γ) events in the inactive gas will, in general, rest only a very few atom layers beneath the surface of the solid; therefore, no matter how irregular the solid is, it should be possible to regard the inert gas as constituting a plane source parallel to the surface of a semi-infinite medium. The plane-source solution of equation [1] can be obtained using the method of images (page 9 of reference 7):

$$[4] \qquad M(x,t) = \frac{M_0}{\sqrt{2\pi kt}}\left\{\exp\left[-\frac{(p-x/\lambda)^2}{2kt}\right]-\exp\left[-\frac{(p+x/\lambda)^2}{2kt}\right]\right\}$$

$$x \text{ and } p = 0, \lambda, 2\lambda, 3\lambda, \ldots ,$$

where M_0 is the source strength (amount/area), p is the position of the source beneath the surface of the solid in units of lattice planes of spacing λ, and x is distance from the surface. Although equation [4] defines $M(x,t)$ for all x and p, only those values of x and p which are integral multiples of λ are of interest. The fractional release now follows as

$$F = (1/M_0)\left\{M_0-\sum_{x=0}^{\infty} M(x,t)\right\},$$

or, if the sum is approximated by the first two terms in the Euler–Maclaurin sum formula (page 25 of reference 8),

$$[5] \qquad F \approx \frac{2}{\sqrt{\pi}}\int_{p/\sqrt{2kt}}^{\infty} e^{-u^2}du \equiv \operatorname{erfc}\frac{p}{\sqrt{2kt}}.$$

F as given by equation [5] is shown plotted as a function of kt (assuming that $p = 1$) in Fig. 3 and as a function of temperature in Fig. 4. It is apparent that equation [5] fails to reproduce the experimental behavior, both as regards the plateaus and also as regards the wide temperature range over which the diffusion is significant.

Diffusion of a Plane Source when the Gradient is Unrestricted

A possible reason for the lack of consistency between equation [5] and the experimental results lies in the assumption basic to equation [5] that the gradient is always low. As a matter of fact, the attached inert-gas activity is located very close to the surface of the

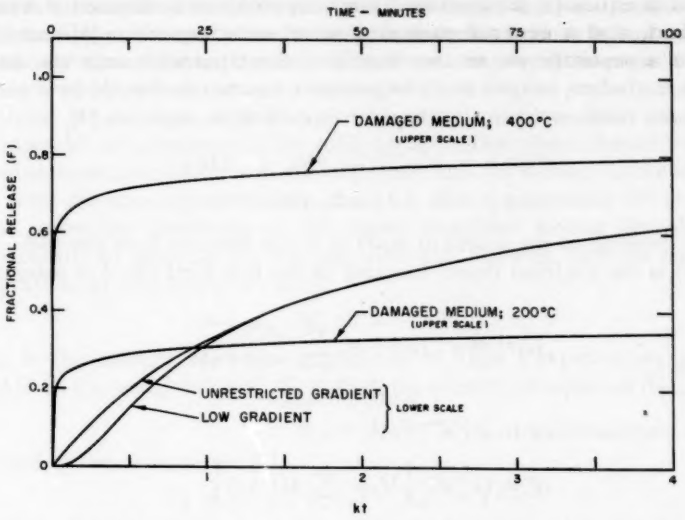


FIG. 3. Theoretical predictions of fractional release as a function of kt or time, derived assuming that the release is a diffusion phenomenon. Three cases are considered: (i) a plane source in a semi-infinite medium when the gradient is always low (equation [5] with $p = 1$), (ii) a plane source in a semi-infinite medium when the gradient is unrestricted (equation [7]), (iii) a source of unspecified nature located in a medium that is extensively damaged, and has composition anomalies, in the region between the source and the exterior (equations [10] or [11] with $k_0 = 10^{13}$ sec^{-1}, $\Delta H_1 = 25$ kcal, and $\Delta H_2 = 60$ kcal).

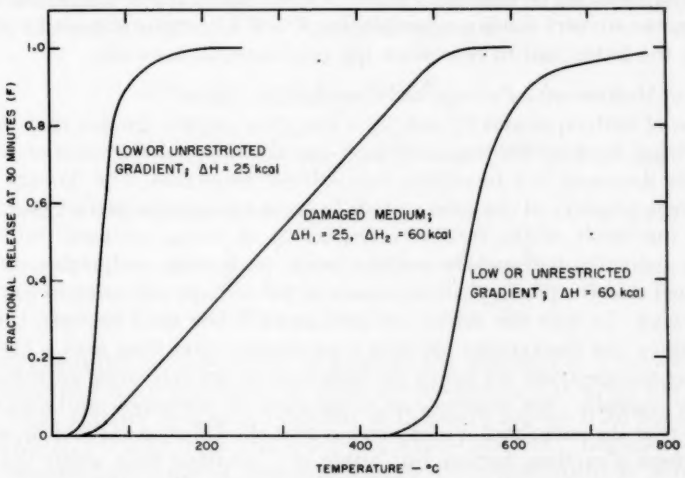


FIG. 4. Theoretical predictions of fractional release at 30 minutes as a function of temperature, derived assuming that the release is a diffusion phenomenon. The same three cases are considered as in Fig. 3, except that equations [5] and [7] have been plotted, not dimensionlessly, but with $k_0 = 10^{13}$ sec^{-1} and $\Delta H = 25$ *or* 60 kcal.

diffusion medium, where extremely high gradients are possible. As a further step in trying to explain the results, one should therefore examine the differential equation which holds for unrestricted gradients (equation [2]).

A solution of equation [2] in closed form has been obtained by Kennedy.[3] A description of the method, and a general comparison of solutions of equations [1] and [2], will be presented in a separate paper, so that for the present purposes only the final results need be given. As before, assume that the geometry can be represented by a plane source in a semi-infinite medium; then, one has corresponding to equation [4],

$$[6] \qquad M(r\lambda,t) = M_0 e^{-kt}\{I_{p-r}(kt) - I_{p+r}(kt)\}$$
$$r \text{ and } p = 0, \pm 1, \pm 2, \pm 3, \ldots,$$

where p is the position of the source in units of λ, r is distance from the surface in units of λ, and $I_n(z)$ is the modified Bessel function of the first kind (9). For integral n, $I_n(z)$ is given by

$$I_n(z) \equiv i^{-n}J_n(iz) = \sum_{u=0}^{\infty} \frac{(z/2)^{n+2u}}{u!(n+u)!}$$
$$I_n(z) = I_{-n}(z).$$

The equation corresponding to [5] is

$$F = (1/M_0)\left\{M_0 - \sum_{r=0}^{\infty} M(r\lambda,t)\right\}$$
$$= 1 - e^{-kt}\{I_0(kt) + I_p(kt) + 2[I_1(kt) + I_2(kt) + \ldots + I_{p-1}(kt)]\},$$

or, for a source located in the first lattice plane beneath the surface of the solid (i.e. $p = 1$),

$$[7] \qquad F = 1 - e^{-kt}\{I_0(kt) + I_1(kt)\}.$$

F as given by equation [7] is shown plotted as functions of kt and temperature in Figs. 3 and 4. The curves are very similar, especially for $F > 0.4$, to those obtained with equation [5], and, like the latter, fail to reproduce the experimental behavior.

Diffusion in a Medium with Damage and Composition Anomalies

A weakness of both equations [5] and [7] is that they neglect the fact that that portion of the solid lying between the attached inert-gas activity and the exterior will tend to be extensively damaged and to exhibit composition anomalies. The damage will be in part an inherent property of the solid surface (a crystal cannot be perfect near a surface), and in part the result of the forcible introduction of foreign material into the solid. Composition anomalies will include surficial oxide, hydroxide, and carbonate layers. It will be assumed that the primary consequences of the damage and composition anomalies are the following: (i) that the activation enthalpies in the solid between the attached inert-gas activity and the exterior occur as a spectrum rather than with a high, discrete value; (ii) that the spectrum lies below the bulk or ordinary activation enthalpy. Further details follow logically: the existence of a *spectrum* of activation enthalpies, coupled with the fact that the enthalpies are *low*, means that the diffusion will not be of the usual type where there is random motion, but rather of a modified form where the release of each inert-gas atom is dependent on *a single rate-controlling jump*. The existence of one-step motion, in turn, means that no assumption about the geometry is necessary.

It should perhaps be pointed out that the assumption that the enthalpy spectrum lies below the bulk enthalpy is reasonable only if damage is the main effect leading to a spectrum. Composition anomalies could give rise to a spectrum extending *above* the bulk

[3]*Private communication from Dr. J. M. Kennedy, Theoretical Physics Branch, Atomic Energy of Canada Limited, Chalk River.*

enthalpy with substances that hold inert gas *less* strongly than the corresponding altered surface layers. Niobium is probably an example of such a substance, since it holds inert gas less strongly than Nb_2O_5 (Fig. 2A). The treatment that follows will, accordingly, be more nearly applicable to systems with very high activation enthalpies, for example, those involving Nb_2O_5, SiO_2, and TiO_2. A high enthalpy is less likely than a low one to be increased by an alteration of the solid surface. (That there should be a difference between substances like niobium, on the one hand, and the oxides, on the other hand, is consistent with the anomaly previously noted for niobium (heading (ii) in Results).)

Diffusion under the conditions of the highly simplified motion described above is governed basically by equation [2]. The equation will, however, lack the terms for interplanar migration, so that one is left with

$$dM_H/dt = -kM_H, \tag{8}$$

where M_H is the amount of diffusing material at time t experiencing an activation enthalpy ΔH. If the initial value of M_H is $M_H{}^0$, the solution of equation [8] can be written

$$M_H = M_H{}^0 e^{-kt},$$

whence, making use of equation [3],

$$\begin{aligned} F_H &= (1/M_H{}^0)(M_H{}^0 - M_H) = 1-e^{-kt} \\ &= 1-\exp(-k_0 t e^{-\Delta H/RT}). \end{aligned} \tag{9}$$

Now introduce the fact that ΔH varies between a minimum, ΔH_1, and a maximum, ΔH_2. While the actual distribution of ΔH is an experimental unknown, it will be sufficient as a first approximation to assume that all values are equally weighted. Also, the dependence of k_0 on ΔH will be neglected (for sinusoidal vibrations of low amplitude, $k_0 \propto \sqrt{\Delta H}$ (5)). Hence, the over-all value for the fractional release is

$$\begin{aligned} F &= \frac{1}{\Delta H_2 - \Delta H_1}\int_{\Delta H_1}^{\Delta H_2} F_H d\Delta H \\ &= 1+\frac{RT}{\Delta H_2-\Delta H_1}\{-\mathrm{Ei}(-k_0 t e^{-\Delta H_1/RT})+\mathrm{Ei}(-k_0 t e^{-\Delta H_2/RT})\}, \end{aligned} \tag{10}$$

where $-\mathrm{Ei}(-z)$ is the exponential integral (9),

$$-\mathrm{Ei}(-z) \equiv \int_z^\infty \frac{e^{-u}}{u}\,du = -\ln \gamma z + \frac{z}{1\cdot 1!} - \frac{z^2}{2\cdot 2!} + \cdots$$

$$\gamma = 1.781\ldots .$$

To use equation [10], it is desirable to simplify the exponential integrals. The experimental temperature range is necessarily *above* the temperature at which the most weakly bound inert-gas activity is readily released. It therefore follows from equation [9] that $k_0 t \exp(-\Delta H_1/RT)$ will be large and $-\mathrm{Ei}[-k_0 t \exp(-\Delta H_1/RT)]$ negligibly small. Similarly, the temperature range is necessarily *below* the temperature at which the most strongly bound inert-gas activity is readily released, so that one obtains

$$-\mathrm{Ei}(-k_0 t e^{-\Delta H_2/RT}) \approx -\ln \gamma k_0 t + \Delta H_2/RT.$$

Hence, for the experimentally interesting temperature range,

$$F \approx \frac{RT}{\Delta H_2-\Delta H_1}\ln \gamma k_0 t - \frac{\Delta H_1}{\Delta H_2-\Delta H_1}. \tag{11}$$

Equations [10] and [11] reproduce the experimental behavior very well indeed, especially with the systems involving oxides (cf. second paragraph in this section). They give plateaus when F is plotted as a function of time (Fig. 3). Moreover, they predict that, for a given value of t, F varies linearly with temperature over a range of temperature which is determined by the values of ΔH_1 and ΔH_2 (Fig. 4). (It is difficult to say whether the expected linearity of F-versus-ln t is also obeyed, because the first 5 to 10 minutes of activity release are perturbed by the effect described in Results.) One concludes that the treatment leading to equations [10] and [11] constitutes a reasonable explanation of the release behavior with which the present work is concerned.

It is perhaps well to restate the main assumptions underlying equations [10] and [11]: (i) the diffusion of inert-gas activity that has become attached near the surface of a solid involves a spectrum of activation enthalpies; (ii) the spectrum lies below the bulk activation enthalpy; (iii) there is approximately equal weighting in the spectrum.

The data of Figs. 2A, 2B, and 2C have been analyzed in terms of equation [11] and values of ΔH_1 and ΔH_2 obtained (Table I). In making the analysis, the deviations from

TABLE I

Activation enthalpies derived using equation [11]

System	ΔH_1* (kcal)	ΔH_2* (kcal)
Ar–Nb or Xe–Nb (powder)	22–28	42–53
Xe–Nb_2O_5 (powder)	25–32	67–85
Xe–SiO_2 (powder)	28–36	68–87
Xe–SiO_2 (rods)	23–30	60–76
Ar–TiO_2 or Xe–TiO_2 (powder)	22–28	58–74
Xe–TiO_2 (balls)	27–34	63–81

*The lower limits of ΔH_1 and ΔH_2 are obtained using the value $k_0 = 10^{11}$ sec^{-1}. The upper limits are obtained with $k_0 = 10^{15}$ sec^{-1}.

linearity in the high-temperature portions of Figs. 2A, 2B, and 2C have been disregarded (cf. heading (ii) in Results). Also, since equation [11] is not sufficiently sensitive to variation in k_0 to yield a value for this quantity, a wide, arbitrary range of values for k_0 was assumed. (Actually, it can be shown that the lower limit of k_0 reproduces the F-versus-ln t behavior somewhat better than does the upper limit.)

(B) General

The success of the theoretical treatment leading to equations [10] and [11] in explaining the observed release behavior of attached inert-gas activity suggests a number of points for discussion.

The Attachment Process

It was shown previously (1) that the attachment process is characterized by the following relations:

$$[12] \qquad \begin{cases} A \ll 1 \\ A_{Ar} > A_{Kr} > A_{Xe} \\ A_{oxide} > A_{metal} \text{ (approximate)}, \end{cases}$$

where A is the attachment efficiency, i.e. the ratio (inert-gas activity attached to target)/(total inert-gas activity). Moreover, it follows from general considerations that the value of A will be governed by the following effects:

(i) *Attachability*—the probability that an inert-gas atom is in a condition to become attached following neutron absorption.

(ii) *Epithermal release*—release that occurs when an inert-gas atom that has entered a solid as if to become attached is immediately expelled due to the existence of a transient epithermal region or hot-spot. Like the epithermal reactions of hot-atom chemistry, this effect would be independent of temperature.

(iii) *Diffusive release*—release that occurs when an attached inert-gas atom diffuses out of a solid after the system has thermalized.

It is of interest to determine whether the present work leads to a correlation between relations [12] and the effects just described.[4]

The relation $A \ll 1$ will obviously be a consequence of all three effects. However, there is some indication that the third effect, i.e. diffusive release, may be of major importance. The argument is based on the fact that the activation enthalpies occur as a spectrum rather than with a high, discrete value as in ordinary diffusion. Assuming that ΔH_1, the *apparent* lower boundary of the spectrum, is merely the minimum barrier height which will retain inert gas at the irradiation temperature, it follows that lower barriers exist, and that a considerable portion of the originally attached inert gas might have experienced such barriers and been subject to diffusive release.[5] Diffusive release also appears to be adequate to explain the relation $A_{\text{oxide}} > A_{\text{metal}}$, for, judging from the values of ΔH_2 for niobium and Nb_2O_5 (Table I), it would seem that attached inert gas is much more tightly bound in an oxide than in a metal.

The remaining relation, $A_{\text{Ar}} > A_{\text{Kr}} > A_{\text{Xe}}$, is probably a consequence of effects (i) and (ii). Diffusive release is ruled out on the basis of the fact that, since argon and xenon show a similar range of activation enthalpies with a given solid (cf. Figs. 2A and 2C), these gases should have comparable probabilities of diffusive release.

The Irradiation Temperature

It has been suggested that inert gas remains attached to a solid only if it experiences a sufficient barrier that it cannot diffuse out at the irradiation temperature. It should therefore be possible to identify the irradiation temperature as that temperature *above which* the rate of release of attached gas becomes significant, for example, the temperature obtained by extrapolating to $F = 0$ a plot of F-versus-temperature. Temperatures in the region of 50 to 150° C are thus indicated for the various solids used in the present work.

The Bulk Activation Enthalpy

The assumption was made earlier that, with certain reservations, the spectrum of activation enthalpies that characterizes the diffusion of attached inert gas lies beneath the bulk or ordinary value, ΔH_{bulk}. One therefore wonders if the upper limit of the spectrum, ΔH_2, is not actually identical with ΔH_{bulk}, i.e.

$$\Delta H_2 \approx \Delta H_{\text{bulk}}. \qquad [13]$$

[4] *A fourth effect, "ejective release", might also be suggested. This is the effect whereby, as the irradiation continues, the incoming inert-gas atoms tend to eject previously attached inert-gas atoms and thus give rise to saturation. That ejective release is not significant in the present work is shown by two facts: (i) saturation is* not *observed (p. 673 of reference 1), (ii) the number of penetrated atoms per unit area in the present work (about 0.0001 monolayer for xenon attaching to an empty quartz capsule when the xenon pressure is 700 mm, the neutron flux 10^{13}, the irradiation time 4 days, and the attachment efficiency 0.0002) is significantly less than the number required for saturation (about 0.1 monolayer for 200 ev ions (10)).*

[5] *The view that the spectrum of activation enthalpies really extends below ΔH_1 is substantiated by a preliminary experiment in which an Ar–TiO_2 mixture was irradiated for 30 seconds at liquid-nitrogen temperature: a factor of 2 increase in A was observed, and the ΔH spectrum extended down to about 10 kcal instead of the usual 22 to 28 kcal.*

Equation [13] should be unaffected by the fact that ΔH_2 was obtained using irregular or poorly crystallized material, since ΔH_2 relates to a process occurring in a region only a few atom layers thick.

Comparison with Other Work

Carter and Leck (10) have recently described work quite closely related to the present work. They bombarded glass with inert-gas ions having energies in the region 80 to 500 ev (cf. Fig. 5 of reference 10), in other words, having the same sort of energies as occur in attachment. (If the attachment of inert-gas atoms is due to the recoil of the atoms following the emission of capture gamma rays, then energies in the region 70 to 210 ev will occur (page 671 of reference 1).) They then caused the inert gas to diffuse out by heating the glass to temperatures up to 350° C. It was concluded, as in the present work, that the diffusion was governed by a spectrum of activation enthalpies. The enthalpy spectrum was found to be the same for neon, argon, krypton, and xenon, to be approximately independent of the ion energy, and to be independent of the thermal history of the glass.[6]

Points of disagreement brought out by the work of Carter and Leck include the following. Carter and Leck assumed that the diffusive motion could be described in terms of a single rate-controlling jump only as an approximation, and did not argue, as in the present work, that a spectrum of activation enthalpies can lead naturally to single-jump motion. They observed a somewhat more restricted range of enthalpies (23 to 45 kcal) than was obtained in the present work for a comparable solid (26 to 68 kcal for SiO_2 rods). They suggested that the existence of a spectrum of enthalpies is attributable to the known heterogeneity of glass, whereas the present work indicates that it is a more general phenomenon, and is, in fact, probably a property of all surfaces.

Comparisons between the present work and ordinary diffusion studies are difficult due to the lack of data. One can point out, however, that the observation that argon and xenon show similar activation enthalpies with a given solid agrees in a general way with the results obtained in studies with silver. Thus ΔH is 33.6 kcal for Ar–Ag (11), 35.0 kcal for Kr–Ag (12), and 37.5 kcal for Xe–Ag (13).

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[6] *A further indication of the close agreement between the present work and that of Carter and Leck lies in the numerical values obtained for the attachment efficiencies. Thus, Carter and Leck observed values of 0.08 to 0.2, depending on the ion energy (cf. the "sticking factors" given in Fig. 5 of reference 10). In reference 1, values of 0.001 to 0.14 were observed for various gases and solids.*

CONSTITUTION OF A GLUCOMANNAN FROM THE SAPWOOD OF SUGAR MAPLE (ACER SACCHARUM)[1]

G. A. ADAMS

ABSTRACT

A glucomannan containing D-mannose and D-glucose in a molar ratio of 7:3 has been isolated from sugar maple sapwood. Electrophorectic examination in acetate and borate buffers showed that the polysaccharide was essentially homogeneous. Methylation and hydrolysis of the glucomannan yielded the following *O*-methyl ethers:

2,3,4,6-tetra-*O*-methyl-D-glucose (1.1%),
2,3,4,6-tetra-*O*-methyl-D-mannose (2.3%),
2,3,6-tri-*O*-methyl-D-glucose (23.4%),
2,3,6-tri-*O*-methyl-D-mannose (65.9%),
2,3-di-*O*-methyl-D-glucose (2.6%),
2,3-di-*O*-methyl-D-mannose (2.7%).

These data in conjunction with periodate oxidation results and estimates of the degree of polymerization indicated that the glucomannan was composed of 25–27 hexose units linked $\beta(1 \rightarrow 4)$ in a linear structure. The chains were terminated predominately by D-mannose units; traces of D-xylose were present in terminal positions only and appeared to be part of the glucomannan molecule.

Although glucomannans from many coniferous woods have been extensively investigated (1), no comparable study of the glucomannans of the hardwoods has been made. The relatively small amount of glucomannan in hardwoods as compared with softwoods has probably contributed to the lack of attention directed to this component. Jones, Merler, and Wise (2) isolated a crude glucomannan from poplar wood which had a glucose:mannose ratio of 1:2 and was a relatively straight-chain polymer with mannose end groups. Hemicelluloses of similar composition have been isolated from Western red alder and madrona by Hamilton and Thompson (3) but their structures have not been determined. A procedure has been developed by Timell (4) for isolation of glucomannans from woody angiosperms and it has been applied to seven species of hardwoods. Detailed structural studies on the glucomannan of white birch (5) and red maple (6) showed that both were composed of approximately 70 glucose and mannose residues linked $\beta(1 \rightarrow 4)$ in linear molecules. The present paper reports the isolation and structural study of a glucomannan isolated from sugar maple sapwood.

Extraction of maple sapwood holocellulose with 24% aqueous potassium hydroxide removed a large proportion of the 4-*O*-methylglucuronoxylans and left the glucomannans in the residue. Further extraction of the residue with 17.5% sodium hydroxide containing 4% borate yielded a crude glucomannan containing also approximately 35% xylan and some galactose residues. Purification of the glucomannan was achieved by forming its insoluble barium hydroxide complex (7) and thereby reducing the xylan impurity to 22%. Precipitation with Fehling's solution caused only a slight change in the mannose: glucose ratio and reduced the xylose content to trace levels in the main fraction. Acid hydrolysis of the hemicellulose and chromatographic examination of the sugars showed glucose and mannose and only a trace of xylose. Unlike many of the glucomannans of softwoods (8, 9, 10, 11), the purified maple glucomannan contained no galactose.

The glucomannan showed a single sharp peak on electrophoresis in borate buffer but electrophoresis in acetate buffer showed a small moving peak in addition to the large stationary peak. Analysis of the materials separated by electrophoresis in acetate buffer

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proved the small peak to be a xylan impurity; the main homogeneous component contained only glucose and mannose. The xylan impurity was not separated from the glucomannan by ultracentrifugation in borate or acetate buffer.

The fully methylated glucomannan was hydrolyzed and an aliquot of the methyl glycosides was analyzed by gas–liquid partition chromatography. The main portion of the methylated sugars was separated on a cellulose column and on paper sheets with the appropriate solvents. The results are given in Table I. The large proportion of

TABLE I

Methylated sugars from hydrolyses of methylated hemicellulose

Methylated sugar	R_g, solvent B	Yield, mg	%
2,3,4,6-Tetra-*O*-methyl-D-glucose	1.0	22	1.1
2,3,4,6-Tetra-*O*-methyl-D-mannose	0.96	45	2.3
2,3,6-Tri-*O*-methyl-D-glucose	0.69	450	23.4
2,3,6-Tri-*O*-methyl-D-mannose	0.63	1270	65.9
2,3-Di-*O*-methyl-D-glucose	0.32	50	2.6
2,3-Di-*O*-methyl-D-mannose	0.28	52	2.7
Di-*O*-methyl-glucose (unidentified)	0.36	15	0.8
2,3,4-Tri-*O*-methyl-D-xylose (?)	0.86	10	0.5

2,3,6-tri-*O*-methyl-D-mannose and 2,3,6-tri-*O*-methyl-D-glucose showed that most of the mannose and glucose units were joined by $1 \rightarrow 4$ glycosidic bonds in the hemicellulose. Negative specific rotations of both the original hemicellulose and its methylated derivative which changed to positive values on hydrolysis indicated a predominance of β linkages. The tetra-*O*-methyl sugars represented non-reducing end groups in the molecule, the ratio of tetra-*O*-methyl-D-mannose to tetra-*O*-methyl-D-glucose (2:1) showed that approximately two thirds of the molecules were terminated by D-mannose units, the remainder by D-glucose. The proportion of tetra-*O*-methyl sugars showed that there was one non-reducing end group for every 27 hexose units. In accord with this value is that of 29 hexose units per reducing end group as found by hypoiodite reduction. Estimation of molecular weight by a vapor pressure method showed that the fully methylated molecule contained approximately 25 units. Since there is only one terminal unit per 27 units (as shown by methylation data), it is apparent that the molecule is a straight chain of hexose units. The dimethyl sugars must have no structural significance and must have been the result of incomplete methylation and(or) demethylation.

On periodate oxidation the consumption of 1.0 mole of periodate per mole of anhydrohexose sugar was further evidence of $(1 \rightarrow 4)$ linked hexose units. Formic acid production of 0.083 mole per anhydro sugar unit indicated a chain length of 25 units in the good agreement with values provided by other methods. Examination of the periodate-oxidized hemicellulose by Smith's degradation procedure (12) yielded erythritol and glycerol as the only products and these must have originated from $1 \rightarrow 4$ linked hexose units and non-reducing terminal hexose units respectively. The ratio of erythritol to glycerol (27:1) provided a further measure of the degree of polymerization (D.P.) of the molecule and the value of 27 is in good agreement with those reported above.

The glucomannans isolated from hardwoods have a wide range of glucose-to-mannose content. Although the general pattern shows a preponderance of mannose over glucose, the glucomannans of elm and sugar maple as reported by Timell (4) had a mannose: glucose ratio of 0.5:1.0. This latter finding is in contrast to that for glucomannan of

sugar maple reported in the present paper (mannose:glucose 7:3). Glucomannans of the coniferous woods have a relatively consistent composition with approximately three times as many mannose as glucose residues (6). It is becoming apparent that galactose may also be an integral part of the glucomannan molecule of softwoods. Galactose has not yet been reported in any hardwood glucomannans and the absence of this sugar may possibly distinguish the hardwood glucomannans from those of softwoods.

The glucomannan of maple sapwood contained approximately 25–27 hexose residues per molecule as compared with 70 residues as found in the glucomannans of white birch (5) and in red maple (6). This variation, which may be attributable to species difference, might also indicate that the glucomannans of the sapwood are smaller than those isolated from the entire woody structure. A further structural difference between the glucomannans of white birch (5) and red maple (6), as compared with that of sugar maple, is the termination of the two former molecules by D-glucose units while two thirds of the molecules of the latter are terminated by D-mannose units. The glucomannan of aspen is also terminated mainly by the D-mannose units (2).

The presence of a small amount of fully methylated D-xylose among the products of hydrolysis from the methylated maple hemicellulose indicated that D-xylose is an integral part of the glucomannan. The methylated xylose did not originate from the small amount of xylan impurity in the original polysaccharide otherwise it would have been 2,3-di-*O*-methyl-D-xylose. A similar association of D-xylose with the glucomannan of jack pine has been reported by Perila and Bishop (13), who obtained oligosaccharides containing xylose and glucose on enzymic hydrolysis. In the maple glucomannan the attachment of xylose is terminal but it is not possible to predict whether it terminates a molecule or is a single unit side branch.

Further work on a larger series of hardwood glucomannans will be necessary to establish not only their composition but also their fine structure and sequence of sugar units.

EXPERIMENTAL

All specific rotations are equilibrium values unless otherwise stated, melting points are corrected, and all evaporations were done at 35° C or less.

Paper Chromatography

Chromatographic separations were carried out using the following solvent systems (v/v):

(A) pyridine: ethyl acetate:water (2:1:2),
(B) methyl ethyl ketone: water: ammonia (100:50:3),
(C) ethanol: benzene: water: ammonia (47:200:14:1),
(D) *n*-butanol: ethanol: water (40:11:19).

Separations were made by the descending method on either Whatman No. 1 or No. 3 MM filter paper. Reducing sugars were located on the paper by the *p*-anisidine spray reagent (14); non-reducing sugar components were detected by silver nitrate and sodium hydroxide sprays (15).

Preparation of the Hemicellulose

A freshly cut log of sugar maple (*Acer saccharum*) was stripped of its bark and the sapwood portion was removed on a veneer lathe. After being air-dried for 48 hours, the thin sheets were passed through a Wiley mill. The milled wood was screened, and the fraction passing through 40 mesh and retained on 100 mesh was used. This wood fraction

was extracted with benzene:ethanol (2:1) for 24 hours, then with ethanol (8 hours), and was dried in air. Extraction with water at room temperature yielded a mixture of water-soluble polysaccharides (0.5%). From the extractive-free wood (1 kg) chlorite holocellulose was prepared (16) in 82.3% yield. Holocellulose (413 g) was stirred in 24% aqueous potassium hydroxide solution (4100 ml) for 6 hours at room temperature in an atmosphere of nitrogen. After filtration the residue was re-extracted once more and then washed with water. While still wet the residue was extracted as above with 17.5% sodium hydroxide containing 4% boric acid (4). The crude hemicellulose was recovered by adding the alkaline extract (9 l.) to the ethanol (24 l.) containing acetic acid (2.4 l.). The precipitate was washed thoroughly with ethanol (80%), the residual ethanol was removed by evaporation, and the crude polysaccharide was recovered by freeze drying (16.5 g). The glucose:mannose:xylose ratio in the polysaccharide was approximately 1:2.5:2 and there was a small amount of galactose present. The sugars were determined by the phenol sulphuric acid method (17).

Purification of the Crude Glucomannan

Crude glucomannan (15 g) was dissolved in 10% sodium hydroxide (750 ml) and 5% barium hydroxide solution (1250 ml) was added slowly with constant stirring over a period of 3 hours. The precipitate that formed was removed by centrifuging, washed twice with water acidified with acetic acid, and poured into ethanol (4 liters). The hemicellulose was recovered by centrifuging, dialysis, and freeze drying. Yield, 8.1 g. The glucose:mannose:xylose ratio was approximately 1:2.5:1.

Further purification of the glucomannan was achieved by forming a series of copper complexes through stepwise addition of Fehling's solution. The complexes were washed sparingly with water, in which they were soluble, dissolved in cold *N* hydrochloric acid, and poured into 5 volumes of ethanol to recover the hemicelluloses. Chromatographic examination of the fractions showed that each contained some xylose in addition to glucose and mannose. Further copper complexing yielded another series of fractions; of these, approximately 60% were pure glucomannans. Galactose and traces of arabinose and rhamnose were in the non-complexing material.

The hemicellulose had $[\alpha]_D^{25} = -24°$ (*c*, 0.76% in 0.5 *N* sodium hydroxide). Hydrolysis for 12 hours with *N* sulphuric acid and examination of the sugars by paper chromatography in solvents A and D showed the presence of glucose, mannose, and trace of xylose. Quantitative determination of sugars (17) in the acid hydrolyzate gave mannose: glucose 7:3. The more accurate method provided by gas–liquid chromatography of the fully methylated sugar as described by Adams and Bishop (18) gave the same value.

Examination of the hemicellulose in 0.05 *M* borate buffer by moving boundary electrophoresis carried out in a Spinco Model H apparatus showed a single peak indicating homogeneity of the polysaccharide. Similar examination in acetate buffer (pH 5.2) (ionic strength 0.2) showed two peaks, a main large stationary peak and a small moving one. Analysis of the separated materials after a migration time of 1020 minutes showed that the large peak represented the glucomannan while the moving peak represented the xylan. Centrifugation of both the borate and the acetate solutions in a Spinco Model E ultracentrifuge at 59,000 r.p.m. showed that each had only a single symmetrical peak. In a separate experiment using a mixture (50:50) of the glucomannan and the acidic xylan it was found that only electrophoresis in acetate buffer gave any separations; no separation was effected in the ultracentrifuge in either borate or acetate buffer.

Periodate Oxidation

Duplicate samples of the hemicellulose (100 mg) were dissolved in water (50 ml) and oxidized by 0.1 *M* sodium metaperiodate (50 ml) in the dark at room temperature. Suitable reagent blanks were prepared under the same conditions. Analyses were made for periodate consumption and formic acid production (19). The results given in moles per mole anhydrohexose unit were as follows.

Time, hours	24	48	72	96	168	216
Periodate consumption	0.57	0.71	0.90	0.91	0.98	0.99
Formic acid production	0.038	0.053	0.064	0.067	0.077	0.083

In a separate experiment the glucomannan (1.0 g) was oxidized by 0.1 *M* sodium metaperiodate (200 ml) at 15.6° C for 23 days. Barium acetate (0.5 *M*) (100 ml) was added to precipitate the iodate and excess periodate, which were removed by filtration. The filtrate was deionized by Amberlite IR-45 and IR-120. Potassium borohydride (1.0 g) was added and the reduction was allowed to proceed for 48 hours. The solution was neutralized with acetic acid, deionized with Amberlite IR-45 and IR-120, and evaporated to dryness several times with methanol. Acid hydrolysis of a portion of the residue and chromatographic examination of the hydrolyzate (solvent A and C) gave two components that were identical with erythritol and glycerol; no monosaccharides were found. Another portion of the hydrolyzate was dried thoroughly *in vacuo*, dissolved in pyridine (15 ml), and acetylated in acetic anhydride (5 ml) at room temperature for 36 hours. The acetylated polyols were examined directly by gas–liquid partition chromatography (8) (using 4′ apiezon M, 20% on celite 545, 197° C, 40 ml helium per minute). The acetates under examination had the same retention volumes as authentic samples of glycerol triacetate and erythritol tetraacetate respectively, and hence their identity was established. The ratio of erythritol to glycerol was 27:1.

Methylation of the Hemicellulose

Hemicellulose (5.0 g) was dissolved in 20% sodium hydroxide (60 ml) and methylated by dropwise addition of dimethyl sulphate (50 ml) and 45% sodium hydroxide (100 ml). The methylation procedure was repeated six more times. The partially methylated material was recovered by chloroform extraction of the neutralized solution, yield 6.8 g. The product was methylated once with Purdie's reagents using methyl iodide (100 ml) and silver oxide (11.5 g), yield 6.14 g, MeO, 35.6%. The product (6.1 g) was methylated by the Kuhn procedure (20) using dry dimethyl formamide (120 ml), methyl iodide (50 ml), and silver oxide (45 g), the solution being shaken for 48 hours at room temperature. The methylated hemicellulose was recovered by the described procedure (20), yield 3.80 g. Infrared spectroscopy showed the presence of hydroxyl groups. Methylation by Purdie reagents, repeated 3 times, gave a product having a methoxyl content of 44.3%, and no hydroxy bands in the infrared spectrum, yield 3.72 g. Fractionation from chloroform solution by addition of light petroleum gave a white product, wt. 3.60 g, $[\alpha]_D^{25}$ −16.3 (*c*, 1.04% in chloroform), methoxyl, 44.9% (theoretical for fully methylated hexosan 45.6%).

Methanolysis and Hydrolyses of the Methylated Hemicellulose

Methylated hemicellulose (1.93 g) was refluxed in 4% methanolic hydrogen chloride (45 ml) for 21 hours. After removal of the solvent the glycosides were hydrolyzed by heating for 20 hours in 0.5 *N* hydrochloric acid. The acid was neutralized with silver carbonate and the methylated sugars were recovered as a syrup (1.91 g).

A small portion of the glycoside mixture was examined by gas–liquid partition chromatography (21). The molar ratio of tetra-, tri-, and di-*O*-methyl glycosides was 2:50:3. The ratio of 2,3,4,6-tetra-*O*-methyl-D-mannose to 2,3,4,6-tetra-*O*-methyl-D-glucose was 2:1. Complete methylation of the mixture of tetra-, tri-, and di-methyl glycosides and re-examination of the glycosides by gas–liquid chromatography showed a ratio of tetra-*O*-methyl-D-mannose to tetra-*O*-methyl-D-glucose of 7:3.

Separation of Methylated Sugars

The mixture of methylated sugars ($[\alpha]_D^{25}$ +13°, water) was separated on a cellulose column (38×3.3 cm) using solvent C with a flow rate of 10 ml/15 minute. The tetra-, tri-, and di-methyl fractions separated on the column were separated into their individual component sugars by chromatography on paper sheets using solvents B. The yields of methylated sugars with their R_g values are given in Table I.

Identification of Methylated Sugars

2,3,4,6-Tetra-O-methyl-D-glucose

The crude syrup was taken up in water and clarified with charcoal; its mobility on a paper chromatogram in solvent B and on electrophoresis in borate buffer was identical with authentic 2,3,4,6-tetra-*O*-methyl-D-glucose. The sugar (98.2 mg) was dissolved in methanol (5 ml), aniline (49 mg) was added, and the mixture was refluxed for 2 hours. Fine white needles separated which, on recrystallization from ethyl ether – light petroleum (b.p. 30–60°), yielded 2,3,4,6-tetra-*O*-methyl-*N*-phenyl-D-glucosylamine, m.p. 136–137°, reported value 137–138° (22).

2,3,4,6-Tetra-O-methyl-D-mannose

The syrup had the same R_g value (0.96) in solvent B as an authentic sample of 2,3,4,6-tetra-*O*-methyl-D-mannose. The sugar (133 mg) was dissolved in methanol (5 ml), aniline (67 mg) added, and the mixture was refluxed for 2 hours. Slow removal of the solvent in a desiccator yielded crystals which were recrystallized from ethyl ether – light petroleum to give 2,3,4,6-tetra-*O*-methyl-*N*-phenyl-D-mannosylamine, m.p. 144°, reported value 144–146° (2).

2,3,6-Tri-O-methyl-D-glucose

After clarification with charcoal, the sugar crystallized on slow evaporation of its solution in ethanol–water. Recrystallization from ethanol – ethyl ether – light petroleum yielded 2,3,6-tri-*O*-methyl-D-glucose, m.p. 121° C, $[\alpha]_D^{25}$ +70.0° (*c*, 1% in water); reported values m.p. 121–123, $[\alpha]_D$ +70.0° (23).

Preparation of the 1,4-di-*O*-*p*-nitrobenzoate yielded the crystalline derivative, m.p. 189–190°, recrystallized from methanol, $[\alpha]_D^{25}$ −34° (*c*, 1% in chloroform); reported m.p. is 189–190° (24).

2,3,6-Tri-O-methyl-D-mannose

This sugar had the same mobility on paper chromatograms (solvents B and D) as authentic 2,3,6-tri-*O*-methyl-D-mannose. The 1,4-di-*O*-*p*-nitrobenzoate derivative was prepared and after one recrystallization from methanol had a melting point of 187–188°; reported value 187–188° (24).

2,3-Di-O-methyl-mannose

Mannose was the only sugar found on demethylation with boron trichloride (25). On paper electrophoresis in borate buffer the sugar had the same mobility as 2,3-di-*O*-methyl-D-mannose. Examination by gas–liquid partition chromatography indicated the presence

of 2,3-di-*O*-methyl-D-mannose. The sugar was converted to its 1,4,6-tri-*O*-*p*-nitrobenzoate derivative, which, after several recrystallizations from methanol, had a melting point of 192°, reported value 194° (26).

2,3-Di-O-methyl-D-glucose

This sugar gave only glucose on demethylation (25). It had the same mobility on paper electrophoresis as 2,3-di-*O*-methyl-D-glucose and on examination by gas–liquid partition chromatography (8), its glycosides had a retention volume identical with that of the glycosides of 2,3-di-*O*-methyl-D-glucopyranose. The aniline derivative was prepared as described above and yielded crystalline 2,3-di-*O*-methyl-*N*-phenyl-D-glucosylamine, which, on recrystallization from ethyl acetate, had m.p. 132°; reported value 134° (27).

Other Methylated Sugars

In addition to the di-*O*-methyl sugars identified above, another dimethyl sugar was present in small amounts. It gave glucose on demethylation and, on chromatographic and electrophoretic examination, appeared to be either 2,4- or 2,6-di-*O*-methyl-D-glucose. A sugar having R_g 0.83 (solvent B) and giving a red color with *p*-anisidine spray was recovered in small amounts. On demethylation it gave xylose only. Chromatographic examination (solvent B and C) indicated that it may be 2,3,4-tri-*O*-methyl-D-xylose.

Estimation of Molecular Weight

Two methods were used: (i) end group determination by hypoiodite (28) and (ii) vapor pressure measurements (29, 30).

(i) Triplicate samples of the hemicellulose (100 mg) were dissolved in 2 *N* sodium hydroxide, and 0.1 *N* iodine (10 ml) was added. The solutions, along with suitable blanks, were kept in stoppered flasks in the dark for 2 hours. After acidification of the solution with 2 *N* sulphuric acid, the iodine was titrated with 0.05 *N* sodium thiosulphate. Number average molecular weights calculated from reducing power values were 4400–4700, which corresponds to a D.P. of 27–29.

(ii) The methylated hemicellulose was dissolved in benzene and the difference in vapor pressure between the pure solvent and the solution was measured at concentrations of 7.16, 5.67, 3.79, 1.95, and 1.48% (g/100 g solution) and extrapolated to infinite dilution. Calculation of molecular weight according to Raoults's law gave a value (number average) of 5450 and hence D.P. = 25.

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THE COMPOUNDS $KMnIO_6$ AND $NaMnIO_6$[1]

ILSE REIMER AND M. W. LISTER

ABSTRACT

Two compounds, originally formulated by Price as $Na_2Mn_2I_2O_{11}$ and $K_2Mn_2I_2O_{11}$ have been shown to be $NaMnIO_6.1/2H_2O$ and $KMnIO_6.1/2H_2O$. Consequently they are compounds of tetravalent manganese, a conclusion confirmed by their magnetic susceptibilities, and by their reactions with a variety of reducing agents; the reactions with ferrous ions, iodide ions, sulphur dioxide, hydroxylamine hydrochloride, and hydrazine hydrochloride were examined. Some of the properties of these compounds are described, and their X-ray powder diagrams show them to be analogous to the nickel salts $NaNiIO_6.H_2O$ and $KNiIO_6.1/2H_2O$.

In a relatively early paper, Price (1) described two complex periodates to which he gave the formulae $K_2Mn_2I_2O_{11}$ and $Na_2Mn_2I_2O_{11}$. Since periodates do not seem to form I_2O_{11} groups, these formulae seemed doubtful, a suspicion which was supported by the variable analyses reported in Price's paper. The present paper describes a re-examination of these compounds, which are shown in fact to be $KMnIO_6$ and $NaMnIO_6$, analogous to the nickel compounds $KNiIO_6$ and $NaNiIO_6$, prepared by Ray and Sarma (2). These compounds may contain a small amount of water of crystallization, being again similar in their behavior to the nickel compounds. It will be noticed that Price considered these to be compounds of trivalent manganese, while they are here formulated as containing tetravalent manganese; considerable evidence supporting this is given below.

PREPARATION OF COMPOUNDS

Price prepared these compounds by mixing manganous sulphate (or nitrate) in fairly strongly acidified solution with a similarly acidified solution of sodium or potassium periodate. He gave practically no details of quantities, so that the method described in the present paper is only approximately the same as his. The methods used by us were as follows.

Sodium Manganese (IV) Periodate

Manganese sulphate (8 g) monohydrate was dissolved in about 400 ml of water containing a few drops of sulphuric acid. Sixteen grams of sodium periodate, $Na_2H_3IO_6$, was dissolved in 600 ml of 0.75 *N* sulphuric acid. The solutions were mixed, whereupon a red precipitate gradually separated. The mixture was kept at 40° C for some hours, after which the mixture was filtered through a sintered-glass disk. The product was washed thoroughly with water, and dried over calcium chloride.

With the quantities used above, some manganese remained in solution, in agreement with the over-all equation

$$MnSO_4 + 2Na_2H_3IO_6 \rightarrow NaMnIO_6 + NaIO_3 + Na_2SO_4 + 3H_2O.$$

The quantities chosen were chosen partly to meet the requirements of Price's formula, and partly to avoid other complexes known to occur with excess sodium periodate (3). However, a better yield would probably be obtained with 2 gram-molecules of sodium periodate to 1 of manganese sulphate.

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Contribution from the Department of Chemistry, University of Toronto, Toronto, Ontario.

Potassium Manganese (IV) Periodate

This was prepared similarly using potassium periodate, KIO_4, in somewhat more acid solution (2 to 3 *N* sulphuric acid). A red precipitate formed, which was filtered, washed, and dried, like the sodium salt.

Analysis

The compounds were analyzed as follows. The water of crystallization was determined by heating to constant weight at 110° C. The water was rapidly lost at this temperature, and no appreciable further loss was observed on heating the compounds to 150° C. Iodine was determined by suspending a weighed sample in water, and bubbling in sulphur dioxide till all was dissolved. Silver nitrate was added and the silver iodide was filtered off and weighed. After removal of excess silver by hydrochloric acid, the manganese was determined by adding excess ammonia, filtering off the manganese hydroxide, dissolving this in dilute sulphuric acid, and evaporating to dryness. The residue of $MnSO_4$ was weighed. It was found that the manganese hydroxide dissolved rather slowly in acid, but this was much speeded up by bubbling in a little sulphur dioxide. Sodium or potassium were determined by acidifying the filtrate with sulphuric acid and evaporating it to dryness. Any sodium bisulphate in the residue was removed by adding ammonium carbonate and a little water, and again evaporating to dryness. In some samples the manganese was precipitated as manganese ammonium phosphate and ignited to $Mn_2P_2O_7$; the alkali metal was then found in a separate sample.

Results of the analyses were as follows.

Sodium salt.—Na 8.00, 7.84%; Mn 18.01, 17.87%; I 40.65, 39.8%, H_2O 3.3%. Calculated for $NaMnIO_6.1/2H_2O$: Na 7.42%, Mn 17.72%, I 40.95%, H_2O 2.9%.

Potassium salt.—K 12.24, 13.05%; Mn 16.32, 17.31%; I 39.59, 39.58%, H_2O 4.3%. Calculated for $KMnIO_6.1/2H_2O$: K 12.00%, Mn 16.86%, I 38.93%, H_2O, 2.8%.

These analyses do not, of course, settle the question of the valency of the manganese, since formulae such as $KHMnIO_6.1/2H_2O$ are sufficiently close in composition as to be indistinguishable. The evidence for tetravalent manganese is given in the next section.

VALENCY OF MANGANESE

This was determined from measurements of (i) oxidation equivalents and (ii) magnetic susceptibilities.

1. Oxidation Equivalents

The substances are too insoluble in water to titrate directly, but they react with excess acidified ferrous ammonium sulphate, and the excess can be titrated with potassium permanganate. Since ferrous ions reduce periodate to iodate ions, a formula with tetravalent manganese would require reduction by four ferrous ions per molecule; trivalent manganese would require reduction by three ferrous ions. The results obtained were as follows.

Sodium salt.—Equivalent weight 78.1. Calculated for $NaMnIO_6.1/2H_2O$ 77.5; $NaHMnIO_6.1/2H_2O$ 103.7.

Potassium salt.—Equivalent weight 85.9. Calculated for $KMnIO_6.1/2H_2O$ 81.5; $KHMnIO_6.1/2H_2O$ 109.0.

These results support a formula with tetravalent manganese.

A second equivalent weight can be obtained by adding a known weight of compound to acidified potassium iodide, and titrating the liberated iodine with sodium thiosulphate.

In this case tetravalent manganese will give 10 equivalents per molecule; trivalent manganese will give 9. The results were as follows.

Sodium salt.—Equivalent weight 31.7, 32.6. Calculated for $NaMnIO_6.1/2H_2O$ 31.0; $NaHMnIO_6.1/2H_2O$ 34.6.

Potassium salt.—Equivalent weight 33.2. Calculated for $KMnIO_6.1/2H_2O$ 32.6; $KHMnIO_6.1/2H_2O$ 36.3.

These results also support a formula with tetravalent manganese.

It had been found (3) with similar compounds that a check on the formula could be obtained by bubbling in sulphur dioxide, and after boiling out the excess sulphur dioxide, titrating the acid formed with sodium hydroxide. Bromcresol green was used as indicator to avoid any precipitation of manganese. However, with the present compounds the results were found to be rather variable, and the equivalent weight was always lower than that calculated even for tetravalent manganese. The results were as follows.

Sodium salt.—Equivalent weight 37.9, 36.1. Calculated for $NaMnIO_6.1/2H_2O$ 38.7; $NaHMnIO_6.1/2H_2O$ 44.4.

Potassium salt.—Equivalent weight 36.1, 37.2, 34.5. Calculated for $KMnIO_6.1/2H_2O$ 40.7; $KHMnIO_6.1/2H_2O$ 46.7.

Hence more acid is formed than would be expected; possibly there is some air oxidation of the sulphur dioxide. So far as they go, the results support tetravalent rather than trivalent manganese.

The reactions with two other reducing agents that might similarly produce acid were investigated. Firstly, hydroxylamine hydrochloride was tried, which was found to react with potassium periodate, KIO_4, producing 4 gram-molecules of acid from 1 gram-molecule of potassium periodate:

$$KIO_4 + NH_3OHCl \rightarrow KI + 2N_2O + 6H_2O + 4HCl.$$

Note that this requires oxidation to nitrous oxide. Sodium manganese (IV) periodate also oxidized hydroxylamine hydrochloride, but produced 3.51 gram-molecules of acid from 1 gram-molecule of the complex salt; potassium manganese (IV) periodate produced 3.58. The expectation was 3 gram-molecules (a formula with Mn(III) would give 2.5 gram-molecules of acid):

$$2KMnIO_6 + 10NH_3OHCl \rightarrow 2KI + 2MnCl_2 + 5N_2O + 17H_2O + 6HCl.$$

However, if the nitrogen of the hydroxylamine was converted to elementary nitrogen, the expectation would be 8 gram-molecules, and the most probable conclusion is that the manganese gives some oxidation to nitrogen as well as to nitrous oxide. The closeness of the result to $3\frac{1}{2}$ is probably accidental.

Similarly hydrazine hydrochloride reacts (a little slowly) with potassium periodate thus:

$$KIO_4 + 2N_2H_5Cl \rightarrow KI + 2N_2 + 4H_2O + 2HCl,$$

the amount of acid produced exactly agreeing with this equation. This led to the expectation that 0.5 gram-molecule of acid would be produced by 1 gram-molecule of sodium manganese (IV) periodate (Mn(III) would give 0.25 gram-molecule):

$$2NaMnIO_6 + 5N_2H_5Cl \rightarrow 2NaI + 2MnCl_2 + 5N_2 + 12H_2O + HCl.$$

However, it was found that addition of the complex salt to a solution of hydrazine hydrochloride (adjusted to the neutral point of bromcresol green or methyl orange) made the solution alkaline, and it remained so even on boiling. If acid was added till the

neutral point of the indicator was again reached, the solution produced more acid spontaneously, and this was then titrated with sodium hydroxide. The total effect was that 1 gram-molecule of the complex salt did in fact produce nearly 0.5 gram-molecule of hydrochloric acid: $NaMnIO_6$ gave 0.61 gram-molecule, and $KMnIO_6$ gave 0.51 gram-molecule of acid. There is evidently a slow stage in the reaction which is catalyzed by acid. Hence both the reactions with hydroxylamine hydrochloride and hydrazine hydrochloride, though not too clear cut, support a formula with tetravalent manganese.

2. Magnetic Susceptibilities

The magnetic susceptibilities of the compounds were measured on a Goüy balance at room temperature. The balance was calibrated with ferrous ammonium sulphate. The observed susceptibilities were: $NaMnIO_6.1/2H_2O$, 23.42×10^{-6} e.m.u./g at 24.8° C; $KMnIO_6.1/2H_2O$, 18.20×10^{-6} e.m.u./g at 22.5° C. If the compounds obey Curie's law, these results make the magnetic moments: sodium salt 4.17 Bohr magnetons; potassium salt 3.76 Bohr magnetons. These are evidently close to the calculated 'spin only' value of 3.87 Bohr magnetons for three unpaired electrons, which would be present in manganese (IV).

PROPERTIES OF COMPOUNDS

The sodium and potassium salts are both red microcrystalline solids. They are virtually insoluble in water, the solubilities not being above 10 mg/liter at room temperature. Consequently no absorption spectrum in solution could be obtained. As mentioned in the description of the analysis, they readily lose their water of crystallization at 110° C, but the anhydrous salts are stable up to a much higher temperature: no decomposition was apparent at 230° C, though iodine vapor was evolved at a red heat. They show no tendency to decompose in water to give permanganate ions, as the complex salts containing more periodate do (3); this is true of suspensions either in water or alkali: in neither case was any reaction apparent on prolonged standing.

STRUCTURE OF COMPOUNDS

Debye–Scherrer X-ray diffraction photographs were obtained from the powdered compounds in the usual way. Similar photographs for $NaNiIO_6.H_2O$ and $KNiIO_6.1/2H_2O$ were obtained at the same time. The nickel compounds were prepared by the method

TABLE I

Interplanar spacings from X-ray powder diagrams

$KNiIO_6$	$KMnIO_6$	$NaNiIO_6$	$NaMnIO_6$
6.00 s	5.93 s	5.12 s	5.12 s
4.29 m	4.29 m	4.29 m	4.31 m
3.52 s	3.49 s	3.30 s	3.30 s
3.03 w	3.04 vw	—	—
2.48 m	2.50 w+	2.49 m	2.49 m
2.30 m	2.30 m	2.24 s	2.25 m
2.02 w+	2.04 m	1.99 m−	2.02 w+
1.91 m	1.91 vw	—	—
1.82 w−	1.77 vw	1.79 m	1.81 m
1.62 vw	1.61 w	—	—
1.56 w+	—	1.56 m−	1.55 w+
1.47 w−	1.46 vw	—	—
1.43 w−	1.42 vw	1.43 w+	1.44_5 w+
1.39 vw	—	1.38 w+	1.41 vw
1.29 w	1.31_5vw	1.28_5vw	1.26 vw

NOTE: s = strong; m = medium; w = weak. Spacings in Å.

given in *Inorganic syntheses* (4). It may be mentioned in passing that while these hydrated formulae are given for the nickel compounds, the reported analyses are closer to the anhydrous salts, especially for the potassium compound. This is doubtless due to the relatively weak attachment of the water, as with the manganese compounds. The object of the present X-ray work was to demonstrate a similarity between the manganese and nickel compounds, which would be expected from their formulae; it is hoped to obtain a more detailed picture of their structure shortly. The values of the interplanar spacings, calculated from the observed lines, are given in Table I. These were obtained using copper K_α X-rays, and a camera of 114.6-mm diameter. The patterns for the corresponding manganese and nickel compounds show considerable similarity, and there can be little doubt that the compounds are isomorphous. This also supports the view that tetravalent manganese is present. The interplanar spacings are not far from what would be calculated for a cubic unit cell, particularly in the case of the potassium salts. This suggests that both the metal and iodine atoms are octahedrally co-ordinated to the oxygen atoms, giving a polymerized structure that would explain the insolubility of these compounds.

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REACTION OF OXYGEN ATOMS WITH BENZENE[1]

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ABSTRACT

The reaction of benzene with oxygen atoms produced by mercury photosensitized decomposition of nitrous oxide has been studied in a circulating system at room temperature. The main reaction product is a non-volatile material probably largely aldehydic in character. This is tentatively assumed to result from the rearrangement and polymerization of the initially formed adduct. Smaller amounts of phenol and carbon monoxide are also formed. The rate of formation of carbon monoxide decreases with increasing pressure, suggesting an energy-rich precursor.

Oxygen atoms react with benzene much more slowly than with olefines. At 120° cyclopentene reacts about 150 times more quickly than benzene. The activation energy of the reaction of oxygen atoms with benzene has been estimated at 4.6 to 4.9 kcal/mole, with an uncertainty of about 0.7 kcal/mole.

INTRODUCTION

Reactions of a number of unsaturated hydrocarbons with oxygen atoms generated by the mercury photosensitized decomposition of nitrous oxide have been studied in some detail in this laboratory, but attention has previously been concentrated on alkenes and cycloalkenes (1–3). The present investigation is a further stage in these studies and has been undertaken in an attempt to derive some information on the attack of ground state oxygen atoms on an aromatic nucleus. Unfortunately, the major part of the reaction product, a polymeric material of low volatility, could not be characterized; only a fragmentary picture of the process has therefore been obtained. This is in sharp contrast to the relatively well-understood major features of the reactions of oxygen atoms with alkenes.

Early attempts to obtain approximate values of the rates of reactions of a number of compounds with oxygen atoms (4) led to the conclusion that benzene reacted very rapidly with oxygen atoms. In the present work, however, this reaction is found to be much slower than the corresponding reactions of alkenes. In view of the electrophilic character of oxygen atoms (3), this finding is not unexpected.

Several workers (4–7) have investigated the reaction of benzene with oxygen atoms generated in electrical discharges. Chu, Ai, and Othmer (8) used a flow system and generated oxygen atoms by electrical discharge in molecular oxygen. They obtained phenol yields of up to 13% per pass, in substantial agreement with the previous findings of Avramenko and co-workers (7). However, with water vapor instead of oxygen discharge they found no detectable amount of phenol although Avramenko *et al.* claimed yields of up to 27% under similar conditions.

The presence of other reactive species and the need to maintain relatively low over-all pressures seriously complicate the use of electrical discharges in molecular oxygen or in water vapor for fundamental studies of the reactions of oxygen atoms with organic compounds. Some of the potential complexities have been discussed elsewhere (8) in connection with a study of the reaction of oxygen atoms produced by electrical discharge in molecular oxygen with 1-butene.

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In the present work oxygen atoms were generated by the mercury photosensitized decomposition of nitrous oxide (9). At not too elevated temperatures nitrous oxide reacts extremely slowly with oxygen atoms in their ground state and with other free radicals. In the presence of benzene the process can be represented by the following reactions:

$$Hg(^1S_0) + h\nu\ (2537\ \text{Å}) \longrightarrow Hg(^3P_1), \quad [1]$$

$$Hg(^3P_1) + N_2O \longrightarrow N_2(^1\Sigma) + O(^3P) + Hg(^1S_0), \quad [2]$$

$$O(^3P) + C_6H_6 \longrightarrow \text{products}. \quad [3]$$

Depending on the quenching efficiency of benzene and on the relative pressures of benzene and nitrous oxide present, there may also be appreciable quenching of $Hg(^3P_1)$ atoms by benzene. However, Scott and Steacie (10) have investigated the mercury photosensitized reactions of benzene and found that appreciable reaction occurs only at higher temperatures. In agreement with this no products due to quenching by benzene have been detected in the present work. The amount of nitrogen formed in reaction [2] serves as an internal actinometer and is used as a measure of the number of oxygen atoms generated.

EXPERIMENTAL

A conventional vacuum apparatus was used, with stopcocks replaced by mercury cutoffs where necessary to prevent the absorption of hydrocarbons by tap grease. The cylindrical quartz reaction cells were 10 cm long and 5 cm in diameter. Early experiments were made in a system of approximately 450 ml in volume, which included an all-glass plunger-type circulating pump. Later, a second reaction cell was added. This was connected to the vacuum line through a metal "Hoke" valve and gave a reaction volume of about 200 ml.

The analysis line contained a Le Roy still (11), a pumped-down trap, and a diffusion pump delivering into a Töpler pump and thence into two gas burettes. One of these latter was greaseless and the other was connected to a small combustion furnace packed with copper oxide. Non-volatile polymeric products remaining in the reaction cells were either extracted by solvents or combusted to carbon dioxide, which was then measured. The low-pressure mercury vapor lamp was run at a constant current of 100 ma, and most experiments were made at 25° C.

Benzene (Nichols reagent grade) was dried over calcium hydride and given several bulb-to-bulb distillations, with rejection of light and heavy fractions on each transfer. It was stored over calcium hydride in a bulb closed by a mercury cutoff. Nitrous oxide (98%) (Matheson Co.) was purified by bulb-to-bulb fractionation. Cyclopentene (Phillips research grade) was passed through an activated alumina column to remove peroxide contamination and then further purified by bulb-to-bulb fractionation. All reactants were degassed before each run.

Nitrous oxide with benzene was irradiated for periods of between 10 minutes and several hours. The reactor was then cooled in liquid nitrogen and the non-condensable gases were collected for analysis by combustion and mass spectrometry. The condensed material was removed to the Le Roy still for fractionation, a process which was normally abbreviated in later experiments to a separation of nitrous oxide at −80° C or −120° C. The fractions of least volatility from the Le Roy still, including unreacted benzene, were subjected to a variety of analytical procedures.

RESULTS

Preliminary experiments showed that non-condensable gaseous products always contained some carbon monoxide but no significant quantities of hydrogen or methane. Spot tests (12) of the condensable products gave a positive reaction for phenol but showed absence of acetylene and formaldehyde. An opaque yellow film on the walls of the reaction cell and a pronounced decline in nitrogen production with time indicated the formation of important quantities of a non-volatile product. The amounts of carbon dioxide formed by combustion of this material proved it to be sufficient in quantity to be a major product of the reaction.

In order to determine more accurately the quantity of non-volatile product by combustion and subsequent measurement of the carbon dioxide evolved, a static reactor which could be heated to redness almost in its entirety was built. Several experiments were carried out with approximately equal initial concentrations of benzene and N_2O but with different irradiation times. The results are shown in Table I.

TABLE I

Effect of the extent of reaction on the ratios R_{CO}/R_{N_2}, $R_{CO_2}/6R_{N_2}$, and $-R_{C_6H_6}/R_N$. (temperature 25±2° C)

Run	C_6H_6 (mm)	C_6H_6 (μmole)	N_2O (mm)	Irradiation time (min)	ΔN_2[a] (μmole)	$\frac{R_{CO}}{R_{N_2}}$	$\frac{R_{CO_2}}{6R_{N_2}}$	$\frac{-R_{C_6H_6}}{R_{N_2}}$
12	6.75	76.3	204	15	10.5	0.172	0.21	n.d.
13	9.54	109.4	199	30	19.4	0.174	0.27	n.d.
14	7.31	83.9	~200	31	20.1	0.176	0.26	0.43
15	7.91	90.8	206	90	48.4	0.175	0.30	0.43
16	7.55	81.8	~200	80	44.4	0.177	n.d.	0.46

NOTE: n.d. = not determined.
[a]Any CH_4 present is neglected.

It is evident from Table I that within the investigated range R_{CO}/R_{N_2} is independent of the extent of reaction, as measured by the amount of N_2 produced. The amount of non-volatile material ($R_{CO_2}/6R_{N_2}$), on the other hand, appears to increase somewhat with increasing conversion. In three of the experiments in Table I, runs 14, 15, and 16, the consumption of benzene per oxygen atom consumed ($-R_{C_6H_6}/R_{N_2}$) has been determined. This was done by recovering the unreacted benzene and measuring it both manometrically and by G.L.C. At these relatively low partial pressures of benzene the number of moles of benzene consumed per gram-atom of oxygen was found to be considerably lower than unity. Comparison of runs 14 and 15 shows the benzene consumption under these conditions to be approximately independent of the extent of reaction.

The early experiments indicated that the production of carbon monoxide decreased as the over-all pressure in the system was increased, as shown in Table II, A. However, in these experiments the partial pressure of benzene was also varied. A separate series of experiments was therefore carried out in which the partial pressure of benzene and the extent of reaction were kept approximately constant. The results are shown in Table II, B, and in Fig. 1 and they confirm a distinct decrease in the carbon monoxide formation with increasing over-all pressure.

In order to obtain some quantitative information on the amounts of phenol formed, two runs were carried out with larger partial pressures of benzene and relatively long irradiations. In this manner high percentage conversions of benzene were avoided.

TABLE II

Effect of total pressure on the ratio R_{CO}/R_{N_2}
(in A are given the mean values of the rates of CO formation from sets of two or more experiments at approximately constant partial pressure of benzene. Temperature 25±2° C)

Run	Total pressure (mm)	C_6H_6 (mm)	N_2O (mm)	Irradiation (min)	ΔN_2 (μmole)	R_{CO}/R_{N_2}
A						
21, 22	55	1.8	53	5, 10	3.22[a], 7.11[b]	0.231±0.003
12, 13, 14, 15, 16	210	7.8	202	15–90	10.5–48.4[c]	.175±.003
24, 25	586	82	504	12, 30	4.45, 9.80[d]	.115±.020
B						
190	49.1	5.67	43.4	70	19.4	0.239
192	106.3	6.19	100.1	85	24.1	.215
188	151.3	4.75	146.5	60	24.8	.195
191	351.1	5.55	345.5	80	27.5	.166
187	504.0	5.28	498.7	60	29.0	.150
189	591.6	5.63	586.0	65	25.2	.143

[a]From run 21.
[b]From run 22.
[c]As shown in Table I.
[d]From run 25.

Fractions recovered from the Le Roy still at −80 to +25° C after these runs (Table III) were each quantitatively diluted with benzene and analyzed by infrared spectroscopy.

TABLE III

Yield of phenol in the reaction of oxygen atoms with benzene
(temperature 25±2° C)

Run	C_6H_6 (mm)	N_2O (mm)	ΔN_2 (μmole)	ΔC_6H_5OH (μmole)	$\frac{\Delta C_6H_5OH}{\Delta N_2}$	$\frac{-\Delta C_6H_5OH}{\Delta C_6H_6}$
19+20	~26	490	64.5	3.6±0.7	0.056±0.011	0.127±0.025
28	83.1	505	640	40±4	0.062±0.006	0.141±0.014

As shown in Table III, some 13% of the benzene consumed during the reaction was found to be converted to phenol. Although the amount of nitrogen produced in run 28 is about 10 times larger than in the combined runs 19 and 20, the amount of phenol formed per gram-atom of oxygen consumed is, within the analytical uncertainty, the same in the two cases.

The non-volatile polymeric material evidently represents the major product of the reaction of oxygen atoms with benzene. Attempts were made to obtain some information on the nature of this material, but with relatively little success. Carbon tetrachloride washings of the reaction cell after runs 27 and 28 were colorless, showed absorption peaks at 279, 272, and 267 mμ in the ultraviolet, and gave a positive reaction to both Brady's reagent and Schiff's reagent, the compound formed with Brady's reagent being soluble in carbon tetrachloride. The presence of aldehyde groupings in this fraction was thus strongly suggested. The reaction cell was subsequently extracted with acetone, which appeared to dissolve the bulk of the deep yellow component of the deposit. The ultraviolet absorption showed single sharp peaks at 323.5 mμ. An infrared spectrum of the acetone extract deposited on a KBr pellet showed a heavy general absorption with a set of broad peaks superimposed at 694, 757, 1225, 1490, 1591, 1667, 1705, 2860, and 3300

cm^{-1} suggestive of aliphatic rather than aromatic groupings. After careful removal of acetone, these extracts also gave, with Brady's reagent, a definite orange color extractable in carbon tetrachloride.

After extraction with carbon tetrachloride and acetone, combustion of the remaining material showed that the two solvents removed only about 50% of the polymeric deposit.

An approximate carbon balance can be obtained for runs 14 and 15 of Table I. Taking $100\ (R_{CO}+R_{CO_2})/6R_{C_6H_6}$ as an approximate measure of the carbon balance, a mean value of about 72% is arrived at. However, the phenol produced ought to be added to this figure. Table III shows amounts of phenol which on the basis of the benzene consumption in runs 14–16 would indicate that about 13 to 14% of benzene is converted to phenol. However, the data in Table III were obtained at much higher partial pressures of benzene and it is conceivable that the consumption of benzene, $-R_{C_6H_6}/R_{N_2}$, under such conditions is closer to unity. In view of this the mean carbon balance for runs 14 and 15 comes to about 75 to 85%. Deposition of non-volatile tarry material in the gas burette used for storing the volatile products, together with the characteristic odor, slight color, and positive reaction to Schiff's reagent of these, suggested that unidentified lower molecular weight products of a very reactive and possibly aldehydic nature were formed. Such products must have been responsible, at least partly, for the failure to obtain 100% carbon balance.

The rate constant of reaction of oxygen atoms with benzene (k_B) relative to that of cyclopentene (k_C) was determined by the competitive technique described in detail elsewhere (3). This technique is based on the measurement of the decline in ethylene production from the reaction of oxygen atoms with cyclopentene when another substance which consumes oxygen atoms is added. Early experiments showed that at room temperature cyclopentene reacted more than 200 times as fast as benzene. It was consequently very difficult to obtain quantitative competitive data. A number of determinations were therefore made at two higher temperatures and the mean values of k_C/k_B obtained were 152.6 ± 13.9 at 119.8° C, and 54.3 ± 4.6 at 220.4° C. The relatively large mean deviations resulted from the large disparity in the rates and from the use of small partial pressures of cyclopentene in order to maintain large benzene to cyclopentene ratios. High partial pressures of benzene were used (close to the saturation pressure at room temperature) and the assumption was made that, under these conditions and at the higher reaction temperatures of these experiments, oxygen atoms were consumed only in the primary attack on benzene and cyclopentene.* Using Arrhenius' equation, the mean values of k_C/k_B at the two temperatures give $E_C-E_B = 4.0$ kcal/mole and $A_C/A_B = 1.0$. It has been established (13) that $E_C-E_{TME} = 0.6$ kcal/mole (where the subscript TME stands for tetramethyl ethylene) and E_{TME} is probably quite small (perhaps not greater than 0.1 to 0.3 kcal/mole) so that $E_B \approx 4.6$ to 4.9 kcal/mole. The experimental uncertainty in this value is estimated from the mean deviations in k_C/k_B at the two temperatures at about ±0.7 kcal/mole.

DISCUSSION

Two modes of attack of atomic oxygen on benzene are possible: abstraction of a hydrogen atom or addition to the aromatic nucleus. Abstraction of a hydrogen atom would lead to the formation of a hydroxyl radical and a phenyl radical. Attack of benzene by hydroxyl would then be expected, with the subsequent production of diphenyl and phenol by radical association according to the following scheme (14).

**A slight thermal reaction occurs at 220° C but this was found to be unimportant under the experimental conditions used.*

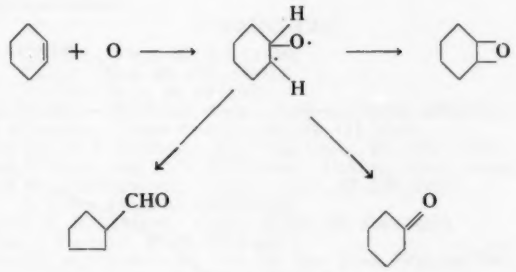
$$C_6H_6 + O \rightarrow C_6H_5\cdot + OH\cdot \quad [4]$$

$$C_6H_6 + OH\cdot \rightarrow C_6H_5\cdot + H_2O \quad [5]$$

$$C_6H_5\cdot + OH\cdot \rightarrow C_6H_5OH \quad [6]$$

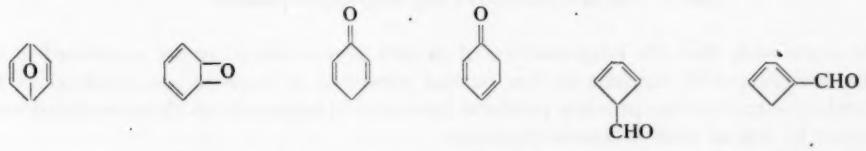
$$C_6H_5\cdot + C_6H_5\cdot \rightarrow \text{diphenyl} \quad [7]$$

Alternatively, as with the olefins and cyclo-olefins, the oxygen atom may add directly to the benzene molecule. Cyclohexene reacts in this fashion to produce a biradical which quickly rearranges to a mixture of cyclohexene oxide, cyclohexanone, and cyclopentyl formaldehyde (2).



[8]

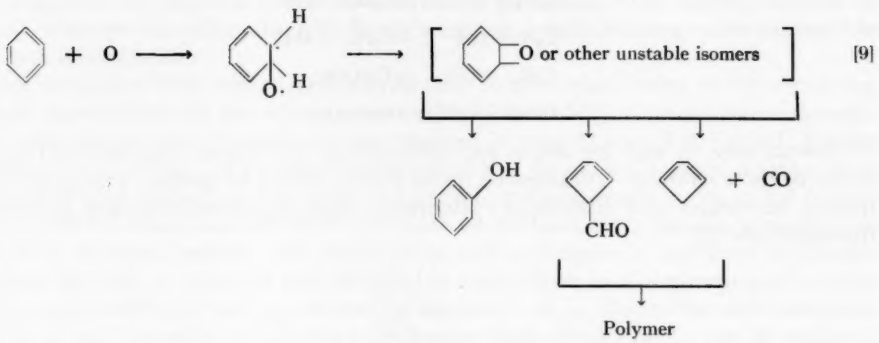
The analogous scheme for benzene presents a larger number of possibilities, as shown below, since in principle either 1:2 or 1:4 addition may occur (although in the case of 1,3-butadiene only 1:2 addition of oxygen atoms is observed (15)).



I II III IV V VI

However, none of these compounds is reported in the literature although some derivatives are known. This is probably because I, II, III, and IV isomerize quickly to the stable structure of phenol whilst V and VI are undoubtedly prone to a variety of condensations and polymerizations.

On the basis of the present experimental results it is clearly impossible to suggest a definite reaction mechanism. It would, however, appear likely that initially an addition complex is formed between an oxygen atom and a benzene molecule and that this becomes in part stabilized as phenol. A larger fraction of the complex, on the other hand, suffers rupture of the aromatic ring with production of unsaturated aliphatic compounds, perhaps such as cyclopentadienyl formaldehyde, which readily undergo further reactions to form non-volatile polymeric material. Such a mechanism is analogous to the attack of oxygen atoms on olefins (2) and is to some extent supported by the type of products observed, the absence of diphenyl, and the pressure effect in the carbon monoxide formation (Table II and Fig. 1). Nevertheless, the evidence is not strong and the proposed mechanism, depicted approximately in the reaction scheme [9], is at present only of a tentative character.



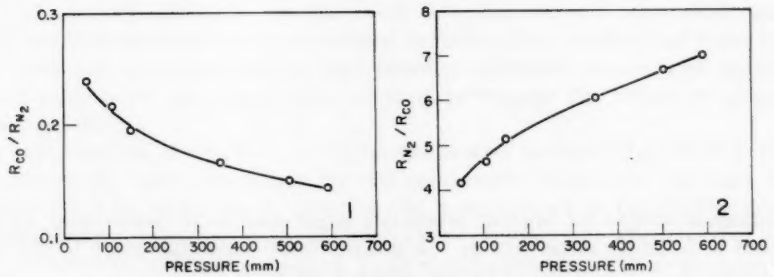


FIG. 1. The effect of pressure on carbon monoxide production.
FIG. 2. Plot of $-R_O/R_{CO}$ (*i.e.* R_{N_2}/R_{CO}) against pressure.

It is probable that the large fraction of oxygen atoms which are not consumed in the initial reaction with benzene at low partial pressures of benzene are involved in the secondary attack on the primary products formed, and especially on those rendered more reactive by loss of their aromatic character.

The pressure effect in the rate of formation of carbon monoxide strongly suggests that this compound is formed from decomposition of an energy-rich adduct as has been observed in the same pressure range in the cases of propylene (2) and 1,3-butadiene (15). With increasing pressure the excess energy tends to be removed by collisions from the "hot" product before it decomposes and carbon monoxide production therefore decreases. Inasmuch as the rate of this collisional deactivation is proportional to the pressure in the system, a linear plot should be obtained by plotting R_{N_2}/R_{CO} against pressure. Actually, as shown in Fig. 2, the plot appears to show a slight curvature. This could be explained by more complex collisional deactivation or by production of carbon monoxide from more than one "hot" species; however, more elaborate treatments are at present not warranted.

In their reactions with olefins oxygen atoms behave as electrophilic reagents (3, 16) and their relative rates are simply related to the basicity of olefins. Insofar as the same holds true for the reactions of aromatic compounds, the much slower rate of reaction with benzene is in qualitative agreement with the observation of West (17) that simple aromatic compounds are generally weaker bases than olefins as measured by the magnitude of the frequency shift of the C—H infrared absorption bands of alcohols or phenols

forming hydrogen-bonded complexes with these compounds. Quantitatively, however, the difference in the reactivity of benzene is much greater than would be anticipated from a comparison of the frequency shifts. Rate data for reactions of oxygen atoms with a number of aromatic compounds are required before these differences can be further discussed.

ACKNOWLEDGMENTS

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REACTION OF OXYGEN ATOMS WITH TOLUENE[1]

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ABSTRACT

The reaction of toluene with oxygen atoms produced by mercury photosensitized decomposition of nitrous oxide has been studied at room temperature. The reaction shows a general similarity to the corresponding reaction of benzene. Relative rates have been determined at 120 and 220° C and the activation energy estimated at close to 4 kcal/mole.

INTRODUCTION

An attempt was recently made in this laboratory to study the reaction of oxygen atoms in their ground electronic state with benzene as the first representative of aromatic compounds (1). Information was obtained on the rate and the activation energy of the reaction, but the major part of the reaction product was unfortunately a material of low volatility which could not be characterized. Therefore only a fragmentary picture of the process was obtained.

The present work was undertaken in the hope of obtaining additional information on the mode of attack of oxygen atoms on an aromatic ring. Another objective was to compare the reactivity of toluene towards oxygen atoms with that of benzene and of unsaturated aliphatic compounds. The relative rate and activation energy of the reaction of oxygen atoms with toluene have been determined but the major reaction product is again a material of low volatility, difficult to handle under conditions used in these experiments. As a result, as in the case of benzene, only a limited amount of information has been obtained on the mechanism of this reaction and in this respect the work has therefore only a preliminary character.

EXPERIMENTAL

A circulating reaction system was used, similar to the one described previously (1). The reaction vessel was a cylindrical quartz cell 10 cm long and 5 cm in diameter. The gases were circulated by means of an all-glass vertical plunger pump. Total volume of the circulating system was 504 ml. Mercury cutoffs were used instead of stopcocks, where necessary, to prevent absorption of hydrocarbons by stopcock grease.

The toluene used was Merck reagent grade, dried over CaH_2, purified by bulb-to-bulb distillation with retention of the middle fraction only, and stored over CaH_2. No impurities could be detected in a sample analyzed by gas chromatography. Nitrous oxide was obtained from Matheson Co. and was further purified by bulb-to-bulb fractionation. Phillips research grade cyclopentene was used. It was freed from peroxides by passage through an activated alumina column, after which it was subjected to bulb-to-bulb distillation *in vacuo*.

The analysis system has been described in the earlier work (1). It incorporated a Le Roy still (2), a Toepler pump, two constant volume burettes, and a copper oxide tube maintained at 240° for combustion of CO and H_2 in the non-condensable gases. Nitrogen

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and methane were recovered from the copper oxide tube unchanged and were further analyzed mass spectrometrically. The amount of CO in the non-condensable gases was estimated from the amount of CO_2 formed in the copper oxide tube and H_2 was found by difference. Ethylene was recovered from the Le Roy still at $-182°$ and contained a small amount of N_2O which was determined by a mass spectrometer and deducted from the total amount of this fraction.

It was difficult to determine toluene consumption accurately since at small conversion this was given as a small difference between two large quantities. Because of relatively low volatility of toluene, direct manometric measurements were not accurate enough and the same held for gas chromatographic determinations. The following technique was found to be better although the experimental uncertainty remained appreciable. Aliquots were taken and the amounts of toluene initially introduced and remaining at the end of a run were determined from the CO_2 produced by combustion (after dividing by 7). For this purpose, oxygen was generated by heating reagent grade $KMnO_4$ and the combustion was carried out for 12 hours on a platinum wire maintained at dull-red heat. After removal of excess oxygen, carbon dioxide was recovered at dry ice temperature and measured. Initially an aliquot was taken from toluene before the introduction of nitrous oxide. At the end of a run, the nitrous oxide was first removed with the Le Roy still kept at $-125°$ after which the toluene and the volatile products (cresols) were allowed to expand again in the reaction volume and an aliquot was taken and combusted. To correct for the cresols present, assumption was made that the aliquot contained the toluene and the cresols in the same ratio as in the bulk retained in the reaction system. The cresols formed were therefore assumed not to exceed their saturation vapor pressures. This assumption was probably valid although there is some uncertainty in the vapor pressure of cresols at room temperature.

The cresols produced in the reaction were determined gas chromatographically. After the removal of N_2O and withdrawal of the aliquot for determination of the residual toluene as described above, all the volatile material remaining in the reaction vessel was distilled over into a small tapered tube immersed in liquid nitrogen and containing a weighed amount (approximately 0.04 g or 40 μl) of a standard solution of an internal standard in a solvent of known concentration. The distilling over was extended for $2\frac{1}{2}$ to 3 hours after which dry air was admitted. Samples of solutions obtained in this manner were analyzed on a Perkin–Elmer 154 C vapor fractometer using 2-meter UCON or, in the later stages of the work, polyester succinate (on chromosorb W) columns at 200° C. Helium was used as carrier gas at a flow of 120 ml/minute. The ratios of peak areas of the *o*- and *p*-cresols to that of the internal standard were determined and compared with those obtained with standard solutions of known concentrations of *o*-cresol, *p*-cresol, and the internal standard. The latter were run between each sample of the solution containing the products of the reaction. With the UCON column the internal standard used was diphenyl and the solvent cumene, and with the polyester succinate column the internal standard was naphthalene and the solvent benzene. The latter column gave better resolution of *o*- and *p*-cresol. The internal standards and the solvents were so selected that the standard was well resolved from the cresols and there was no interference from the large excess of the solvent.

The recovery of cresols was checked by following a $2\frac{1}{2}$-hour distillation for transfer of cresols into the tapered tube with a second 2-hour distillation into a fresh sample of standard solution. No detectable amounts of cresol were recovered in the second distillation.

RESULTS

The products observed in the reaction of oxygen atoms with toluene at room temperature have been *o*-cresol, *p*-cresol, carbon monoxide, water, and a reddish-yellow material of low volatility which was not further characterized (referred to in the following as "polymer").

The identification of the two cresols was based on their gas chromatographic elution times and their infrared spectra. The third isomer, *m*-cresol, was not resolved from *p*-cresol on the columns used. However, the infrared spectra of the condensable volatile products showed that *m*-cresol constituted at most only 4 to 5% of the total cresols and perhaps less. Between about 15 and 20% of the oxygen atoms reacting with toluene (as measured by the amount of nitrogen produced) were recovered as cresols. On the average, about 3–4 times as much *o*-cresol was formed as *p*-cresol.

Water was estimated approximately by gas chromatography. After removal of N_2O, the volatile condensable products were collected and passed at room temperature through a 12-ft dimethyl sulpholane column on glass beads. For water, the peak areas were not linearly related to the amounts taken and the determinations were based on an empirical calibration curve. Relatively long exposures had to be used in order to produce sufficient amounts of water for analysis and the mean of two determinations showed the presence of an amount of water corresponding to 7% of the oxygen atoms reacting with toluene.

Attempts were made to estimate the amounts of non-volatile "polymer" formed by admitting oxygen into the evacuated reaction cell and heating the cell to redness. The carbon dioxide produced was determined and the amount obtained, divided by 7, was taken as the measure of the "polymer" formed. However, the combustion of the "polymer" was not quantitative since it partially distilled and deposited on the walls of the glass tubing outside the reaction cell. Nevertheless, there could be little doubt that this material represented the major part of the reaction product, in agreement with the observed low carbon and oxygen atom balance.

Solutions of the products analyzed gas chromatographically for cresols showed complete absence of dibenzyl. The vapor pressure of dibenzyl at room temperature is approximately one-fifth of that of *p*-cresol and under conditions under which most of the cresol is recovered it would seem reasonable to expect recovery of at least some dibenzyl if an appreciable amount is formed. In view of this it appears that in the reaction of oxygen atoms with toluene, at most only negligible amounts of dibenzyl are formed.

Some of the experimental results are summarized in Table I. In most of these experiments an approximately constant amount of toluene was initially used while the exposure times were varied. Because of "polymer" deposit on the reaction cell window the amount of incident light varied with time and from experiment to experiment. The extent of reaction should therefore be judged from the amount of nitrogen formed rather than from the exposure time. For four- to five-fold increase of nitrogen production no drastic changes in the rates of formation of the products are evident. There is perhaps a slight decrease with the extent of conversion in the rates of cresol formation and toluene consumption, although the experimental scatter is large and makes this uncertain. The average rate found for toluene consumption per oxygen atom is 0.80 but it is difficult to say whether the difference from the expected value of unity is real or due to imperfections of the analytical procedure used. As already mentioned, the values obtained for the "polymer" represent only lower limits.

In these experiments the partial vapor pressure of toluene was relatively high so that some quenching of the excited mercury atoms by toluene did occur. However, this is

TABLE I

Products formed in the reaction of oxygen atoms with toluene
($25\pm2°$ C; p_{N_2O} = 385±5 mm)

Run	Toluene		Time (hours)	N_2 (μmoles)	Relative rates (R/R_{N_2})						
	Initial (μmoles)	Consumed (μmoles)			CO	*o*-Cresol	*p*-Cresol[c]	Polymer	Water	Toluene	*o*-Cresol / *p*-Cresol[c]
23[a]	239.6	25.6	0.5	22.32	0.070					1.15	
22[a]	245.7		0.5	22.94	.066	0.146	0.046				3.2
15[b]	227.7	24.4	2	38.01	.071	.124	.036	0.52		.64	3.4
21[a]	244.8	34.1	1	39.52	.065	.134	.035			.86	3.8
33[a]	285.1	25.3	1.05	39.60	.066	.114	.038			.64	3.0
34[a]	258.2	45.9	1.6	61.34	.068	.114	.035			.75	3.3
16[b]	258.1	49.3	3.25	64.53	.077	.114	.032	.23		.76	3.5
20[a]	260.4	50.1	2.05	64.58	.079	.116	.032	.19		.78	3.6
18[b]	218.9	38.5	3	68.65	.074	.090	.022	.35		.56	4.1
17[b]	271.0	66.7	3	75.05	.071	.094	.024	.14		.89	3.9
19[b]			3	79.74	.057	.128	.034	.11			3.8
27[a]	197.8	73.3	6	107.0	.072					.69	
26			3	72.80	.074				0.076		
28	180.0		5.7	121.6	.062				0.063		

[a]Cresols determined on the polyester succinate column.
[b]Cresols determined on the UCON column.
[c]May contain small amounts of *m*-cresol, as explained in the text.

unlikely to have influenced to any appreciable extent the course of the studied reaction. When toluene alone was subjected to mercury photosensitized reaction for a period of 19 hours, only about 2 μmoles of non-condensable material were collected and of this only about one-third appeared to be combustible. No significant amounts of C_2, C_3, and C_4 fractions were found and infrared analysis of the condensable material in the reaction vessel revealed no significant amounts of products.

The effect of pressure on the products has been studied by varying the partial pressure of nitrous oxide at a constant small pressure of toluene and irradiating for 1 hour. The results are given in Table II. There do not appear to be any drastic changes in the rates

TABLE II

The effect of pressure on the products
(25±2° C; irradiation time 1 hour; cresols determined on the polyester succinate column)

Run	N_2O (mm)	Toluene Initial (μmoles)	Toluene Consumed (μmoles)	N_2 (μmoles)	Relative rates (R/R_{N_2}) CO	o-Cresol	p-Cresol[a]	Toluene	o-Cresol / p-Cresol[a]
29	100	252.1	33.7	35.5	0.093	.142	.053	0.95	2.7
30	221	273.8	35.8	40.8	.077	.145	.046	.88	3.1
21	384	244.8	34.1	39.5	.065	.134	.035	.86	3.8
33	385	285.1	25.3	39.6	.066	.114	.038	.64	3.0
31	683	284.0		48.3	.059	.112	.032		3.5
32	672	333.9	29.7	40.7	.059	.133	.038	.73	3.4

[a]May contain small amounts of *m*-cresol, as explained in the text.

per gram-atom of oxygen (R/R_{N_2}) for a substantial variation in total pressure although small trends could be hidden by the experimental scatter of points. In the case of carbon monoxide the analytical accuracy is greater and there is a distinct decline in the rate of carbon monoxide formed per gram-atom of oxygen consumed (R_{CO}/R_{N_2}) with increasing pressure. This is shown in Fig. 1 and resembles the trend previously observed in the reaction of oxygen atoms with benzene (1).

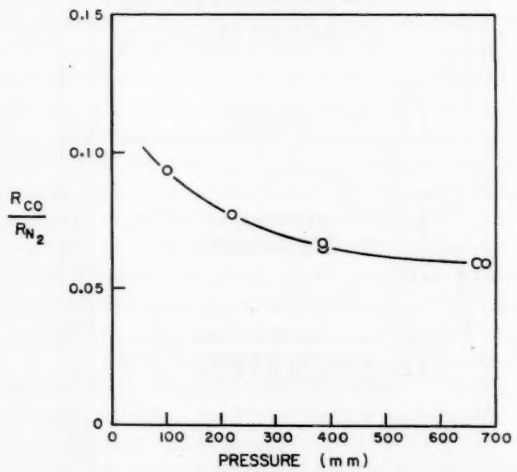

FIG. 1. Pressure effect in the rate of carbon monoxide formation.

The rate constants of reaction of oxygen atoms with toluene (k_T) relative to those of cyclopentene (k_C) were determined at 120 and 220° C by the competitive technique described in detail elsewhere (3). This technique is based on measurements of the decrease in the amount of ethylene formed by attack of oxygen atoms on cyclopentene when another substance consuming oxygen atoms is present. At room temperature it was found that toluene reacted much more slowly than cyclopentene and reliable values of relative rate constants would be very difficult to obtain. At 220° C a very slow thermal reaction producing nitrogen occurred. With the total residence times of the reactants in the reactor under 2 hours the extent of the thermal reaction was almost negligible. Nevertheless, a correction for the very small amount of nitrogen produced thermally was made. No measurable thermal reaction was observed at 120° C.

The relative rate constants (k_T/k_C) obtained at 120 and 220° C are given in Table III.

TABLE III

Determination of relative rate constants of addition of oxygen atoms to cyclopentene (k_C) and toluene (k_T)
(the amounts of reactants and of the nitrogen produced are given in millimeters, in 1107[a] ml at 25° C; the amounts of ethylene are given relative to the nitrogen produced)

Run	Temp. (°C)	N_2O (mm)	Toluene (mm)	Cyclo-pentene (mm)	Irradiation (min)	N_2[b] (mm)	C_2H_4[c]/N_2	k_C/k_T
I. 120° C								
290	120.3	520.4	21.2	2.59	60	0.527	0.239	50.2
291	119.9	523.9	21.3	2.59	60	.509	.245	60.3
292	120.1	523.2	21.0	2.52	62	.541	.243	57.7
293	120.5	520.8	20.6	2.38	60	.473	.244	61.1
Mean	120.2							57.3±3.6
II. 220° C								
287	222.0	409.7	16.4	2.48	60	0.519 (.523)	.209	24.5
288	222.0	411.2	15.9	2.26	60	.520 (.523)	.208	26.0
289	222.4	412.1	15.9	2.52	60	.506 (.509)	.211	24.3
Mean	222.1							24.9±0.7

[a] In these experiments the reaction cell was a 1-liter quartz round flask provided with a glass stirrer on teflon bearings magnetically operated from outside. This larger reaction volume permitted smaller cyclopentene pressures to be used and consequently somewhat larger toluene to cyclopentene ratios.
[b] At 220° C, N_2 values are corrected for thermal reaction; the uncorrected values are given in parentheses to show the extent of the corrections made. No thermal reaction occurred at 120° C.
[c] Several determinations gave for cyclopentene alone (i.e. in the absence of toluene but otherwise under comparable conditions) mean C_2H_4/N_2 ratios of 0.274 and 0.282 at 220 and 120° C respectively. These values were used in calculating the rate constants from equation (5) of reference 3.

The large mean deviations are primarily due to the large disparity in the rates of attack of oxygen atoms on cyclopentene and toluene, respectively. With the practically usable mixtures of the two hydrocarbons under conditions of the present experiments the reaction always occurred predominantly with cyclopentene. As a consequence even slight errors in the measured amounts of ethylene formed caused large errors in the values of the rate constants, especially so at the lower temperature where the disparity in the two rates is greater.

From the mean values of the relative rate constants at 120 and 222° C a difference in the activation energies of attack of oxygen atoms on toluene (E_T) and cyclopentene (E_C) of 3.2 kcal and a ratio of the pre-exponential factors (A_T/A_C) of unity are obtained. In view of the likely value (4) of E_C a value for E_T of about 3.8 to 4.1 kcal/mole is thus arrived at. The mean deviations indicated in Table III introduce an uncertainty in $E_T - E_C$ of ±0.3 to 0.4 kcal and a factor of about 1.5 in the ratio of the pre-exponential

factors. Because of large disparity in the rates between toluene and cyclopentene, as pointed out above, toluene presents an unfavorable case for accurate determination of relative rates by the cyclopentene technique and the margin of uncertainty in $(E_T - E_C)$ and (A_T/A_C) may be even greater.

DISCUSSION

Reaction of oxygen atoms with toluene shows great general similarity with the reaction of oxygen atoms with benzene (1). As in the case of benzene, (1) the major reaction product is a material of low volatility, probably polymeric in character; (2) smaller amounts of phenols are formed; (3) there is a pressure effect in the rate of carbon monoxide formation, suggesting an energy-rich precursor; and (4) products expected for a primary hydrogen abstraction reaction are not detected.

In view of these findings it is most likely, as was postulated for benzene (1), that in the case of toluene also the primary step is an addition of oxygen atoms to the aromatic ring rather than hydrogen abstraction. In agreement with this no dibenzyl is detected. Small amounts of water formed (equivalent to about 7% of the oxygen atoms consumed) could mean that some hydrogen abstraction does occur; however, water could equally well be formed in secondary processes. The initial adduct could be visualized as either being stabilized into cresols or rearranging into products which partially decompose or, to a much greater extent, undergo polymerization. These matters have been speculatively discussed for the benzene reaction (1) and in view of the similarity of the two processes there is no need for further discussion here. Until the nature of the "polymeric" material is established, any attempt to establish the mechanism of these reactions will necessarily remain only speculative.

The pressure effect in carbon monoxide formation is very similar to that observed with benzene (1) although in the case of toluene carbon monoxide is a less important product. As with benzene, the plot of R_{N_2}/R_{CO} is not linear but shows instead a distinct curvature. Smaller production of carbon monoxide from toluene rather than from benzene at comparable pressures may be compared with the formation of fragmentation products in the reaction of oxygen atoms with alkenes. In this latter case, again the "hot" addition products formed by reaction of oxygen atoms with olefins containing a smaller number of carbon atoms (C_2H_4, C_3H_6) are shorter lived and undergo fragmentation much more easily (at comparable pressures) than products from olefins containing a greater number of carbon atoms (5). This is readily understandable in terms of the number of internal degrees of freedom available for dissipation of energy, although the stability of the fragments formed must play also an important role, as evident from the reaction of oxygen atoms with 1,3-butadiene (6).

Formation of large amounts of ortho- and para-cresol and at most of very small amounts of metacresol in the reaction of oxygen atoms with toluene is understandable in view of the electrophilic character of oxygen atoms. Relatively large ortho-to-para ratio is to be noted since it suggests little or no steric hindrance to the addition of oxygen atoms ortho to methyl group. The upper limit for metacresol obtained from infrared spectra seems to be below the amount that would be expected if the "selectivity relationship" for electrophilic substitution reactions of toluene (7) were applicable to the present reaction. However, more quantitative information on metacresol is required before this matter can be further discussed.

The relative rates of addition of oxygen atoms to toluene confirm the previous finding with benzene (1) of a slower attack of oxygen atoms on an aromatic ring than on an

olefinic double bond. At the same time, as expected, toluene reacts appreciably faster than benzene (1). It is of interest that the pre-exponential factors for benzene and toluene appear to be similar to those of olefins (4), although there may be an appreciable margin of uncertainty in the activation energies and pre-exponential factors for the two aromatic hydrocarbons.

ACKNOWLEDGMENTS

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LIGHT ABSORPTION STUDIES

PART XX. THE ULTRAVIOLET ABSORPTION SPECTRA AND INFRARED CARBONYL BANDS OF BENZOYL CHLORIDES[1]

W. F. FORBES[2] AND J. J. J. MYRON[3]

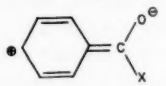
ABSTRACT

The ultraviolet absorption spectra and infrared carbonyl bands of a number of substituted benzoyl chlorides are determined. It is found that as a first approximation the *B*-bands of the ultraviolet spectra are similar for benzoyl chlorides and for the corresponding benzaldehydes and acetophenones. The spectra are discussed in terms of previously stated hypotheses. In this way the order of the apparent negative mesomeric effect is deduced to be $-NO_2 > -COCl > -CHO > -COCH_3$, and the effective size of these substituents is confirmed to be in the order $-NO_2 > -COCH_3 > -COCl > -CHO$.

The infrared carbonyl band occurs as a well-defined doublet in most of the ring-substituted benzoyl chlorides. The most probable explanation is that these doublets occur because of an intramolecular vibration.

INTRODUCTION

In previous parts of this series (see, for example, refs. 1, 2, 3) it was shown that spectral changes in the main ultraviolet absorption band of substituted benzene derivatives could be rationalized by assuming that such changes are predominantly caused by mesomeric and steric interactions, but are not appreciably affected by other short-range interactions such as inductive and field effects. In compounds such as benzoyl chloride, benzaldehyde, and acetophenone this would imply that the main ultraviolet band, the *B*-band (for nomenclature see previous parts of this series and ref. 4), may be associated with resonance forms of type I, which schematically represents mesomeric interactions between the carbonyl group and the benzene ring. If this is correct, the *B*-band of benzoyl chloride should be similar to the *B*-band of benzaldehyde and acetophenone, and should undergo



(I)

X = Cl, H, or CH_3

changes on ring substitution similar to the corresponding *B*-band changes occurring in acetophenone or benzaldehyde on substitution.

The purpose of the present paper is to investigate this hypothesis and also to determine the infrared carbonyl band in substituted benzoyl chlorides. These latter bands are of interest because the infrared carbonyl band of benzoyl chloride is well known to occur as a doublet, the origin of which is unknown. Information concerning the nature of this doublet may thus be provided by investigating this carbonyl band in a number of substituted benzoyl chlorides.

EXPERIMENTAL

The ultraviolet absorption spectra were determined by standard methods in 1-cm cells using a Unicam SP 500 or a Beckman Model DU or Model DK 2 spectrophotometer.

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For each compound at least two independent sets of observations were made. The Unicam SP 500 instrument was calibrated against a didymium filter, and wavelength readings obtained on the Unicam and Beckman instruments were found to be within 1 mμ of each other. The precision of λ_{max} values is estimated to be 1 mμ, and the precision of ϵ_{max} values, 5% or better. Values were reproducible for most compounds to 2%. The main ultraviolet maxima in cyclohexane solution are listed in Tables I and IV. The spectra could not be determined in ethanol solution due to reaction of the benzoyl chloride with the solvent.

The infrared spectra were determined on a Unicam SP 100 double-beam spectrometer with an SP 130 sodium chloride prism-grating double monochromator. The resolution in the 1700 cm^{-1} region was ca. 0.5 cm^{-1}. The solute concentration was kept within the limits of 4.7×10^{-2} and 9.2×10^{-2} mole/liter (usually 0.5-mm cells with KBr windows), except when as otherwise stated. The infrared absorption bands are shown in Tables I, II, and III and in Figs. 3, 5, and 7. Infrared spectra were also used to show the absence of any appreciable amount of acid which might have been formed through decomposition of the benzoyl chlorides.

The benzoyl chlorides were either prepared by standard methods or obtained from commercial sources; they were purified by distillation or recrystallization until their boiling points and refractive indices or melting points showed them to be sufficiently pure. The solvents used were spectroanalyzed cyclohexane (Fisher) or other commercially available spectroanalyzed solvents.

THE ABSORPTION CHARACTERISTICS OF BENZOYL CHLORIDE

The main ultraviolet absorption bands and the infrared carbonyl and adjoining bands of benzoyl chloride and related compounds are shown in Table I.

TABLE I

Absorption spectra of benzoyl chloride and related compounds*

	Ultraviolet absorption bands (in cyclohexane solution unless otherwise stated)				Infrared absorption bands in carbon tetrachloride solution	
	B-band		*C*-band		Carbonyl band	Benzene band
Compound	λ_{max} (mμ)	ϵ_{max}	λ_{max} (mμ)	ϵ_{max}	ν_{max} (cm^{-1})	ν_{max} (cm^{-1})
Benzoyl chloride	242 ca. *250*	14,500 *12,000*	282 ca. *291*	1,300 *900*	1,782 (s)† 1,740 (m)	1,591 (w)† 1,577 (vw)
Benzoyl chloride in ether solution	244	14,300	282–283	1,400	1,784 (s) 1,740 (m)	
Benzoyl chloride in vapor phase	233 237 240.5 242	‡	255 273 276 279 283 287	‡	1,798 (s) 1,756 (m)	1,598 (m)
Benzaldehyde	241 *247*	14,500 *12,500*	277–278 287	1,200 1,000	1,709 (s)	
Acetophenone	237–238	12,500	277	900	1,691 (s)	

*Data from this paper or previous parts of this series.
†Values for the maxima were the same at solute concentration 2.5 *M*, 0.5 *M*, 0.25 *M*, and 0.05 *M* (using different-path-length cells).
‡Intensities not determined.

Table I shows that both *B*- and *C*-bands of benzoyl chloride are similar to the corresponding bands of benzaldehyde and acetophenone, that is, the bands occur at similar wavelength, are not appreciably affected if the ultraviolet spectra are determined in ether solution, do not show an appreciable concentration dependence, and tend to exhibit some fine structure at longer wavelength. (In acetophenone, the fine structure becomes apparent in the vapor phase (2).)

In the vapor phase, benzoyl chloride affords the usual displacement to shorter wavelength (5). All these observations can be rationalized by assuming that as a first approximation the ultraviolet *B*-band is predominantly determined by mesomeric interactions (as crudely represented by resonance forms of type I), to which the chlorine atom does not appreciably contribute.

The infrared carbonyl band, on the other hand, is appreciably affected by the chlorine atom and causes a displacement to higher frequency, compared with the location of this band in benzaldehyde. Conversely, replacement of an hydrogen atom by a methyl group, as in acetophenone, causes a displacement to lower frequency. These displacements can be readily related to the over-all electronegativities of the chlorine atom and the methyl group (cf. ref. 6 and also ref. 7 for the yet higher carbonyl band frequency of benzoyl fluoride). Moreover, the carbonyl band in most benzoyl chlorides exhibits a doublet (see Table II and cf. refs. 8, 9, and 10) which is not appreciably affected either by a change in solute concentration (within the solute concentration range 0.05 to 2.5 *M*) or by determination of the absorption in ether solution (see Table I). Therefore it is unlikely that the carbonyl band doublet is caused by a monomer–dimer equilibrium. Further, neither in the 800–900 cm^{-1} region, nor in the 600 cm^{-1} region, are there absorption bands, overtones, or combination bands which can quantitatively and convincingly account for the observed doublets in all of the benzoyl chlorides (see later discussion). The infrared carbonyl bands of benzoyl chloride and of a number of substituted benzoyl chlorides are listed in Table II. The effect of altering the solvent from chloroform to carbon

TABLE II

The spectral changes of the infrared carbonyl bands with ring substitution (in carbon tetrachloride solution)

Ring substituent	Band *A* ν_{max} (cm^{-1})	Band *B* ν_{max} (cm^{-1})	Ring substituent	Band *A* ν_{max} (cm^{-1})	Band *B* ν_{max} (cm^{-1})
H	1782 (s)	1740 (m)	*m*-Br	1804 (w)	1761 (s)
p-MeO	1777 (s)	1744 (s)	*o*-Br	1795 (s)	1742 (w)*
m-MeO	1776 (s)	1736 (w)	*p*-I	1779 (s)	1736 (m)
o-MeO	1792 (s)	1752 (m)	*m*-I	1797 (m)	1758 (s)
p-F	1786 (s)	1754 (s)	*o*-I	1789 (s)	Shoulder
m-F	1782 (s)	1755 (s)	*p*-NO_2	1793 (m)	1766 (s)
p-Cl	1783 (s)	1742 (m)	*m*-NO_2	1792 (m)	1764 (s)
m-Cl	1818 (w)	1765 (s)	*p*-CH_3	1777 (s)	1744 (m)
o-Cl	1796 (s)	1740 (w)*	*m*-CH_3	1767 (s)	1738 (vw)
p-Br	1779 (s)	1738 (s)	*o*-CH_3	1781 (s)	1737 (w)

*Appreciable fine structure.

tetrachloride and the effect of temperature on the infrared carbonyl band of benzoyl chloride in carbon tetrachloride solution has recently been reported by Jones *et al.* (10). These workers note that the behavior of the infrared carbonyl band under these conditions parallels the behavior of the infrared carbonyl band in a number of unsaturated lactones. Jones *et al.* (10) have also confirmed the absence of any concentration dependence of this band over a 200-fold range.

Benzoyl chlorides also exhibit two infrared absorption bands in the region 1560–1600 cm^{-1} (cf. ref. 11), which are listed in Table III. The generally more intense band near

TABLE III

The infrared spectral changes of the two aromatic vibration bands with ring substitution (in carbon tetrachloride solution)

Ring substituent	Band 1 ν_{max} (cm^{-1})	Band 2 ν_{max} (cm^{-1})	Ring substituent	Band 1 ν_{max} (cm^{-1})	Band 2 ν_{max} (cm^{-1})
H	1591 (w)	1577 (vw)	*m*-Br	1580 (vw)	1562 (w)
p-MeO	1596 (s)	1573 (m)	*o*-Br	1582 (m)	1560 (w)
m-MeO	1592 (m)	1582 (w)	*p*-I	1574 (m)	1559 (w)
o-MeO	1596 (s)	1582 (m)	*m*-I	1578 (vw)	1559 (w)
p-F	1594 (s)	—	*o*-I	1574 (m)	1557 (w)
m-F	1588 (m)	—	*p*-NO_2	1601 (m)	—
p-Cl	1584 (m)	—	*m*-NO_2	1609 (m)	1582 (vw)
m-Cl	1591 (vw)	1576 (w)	*p*-CH_3	1603 (m)	—
o-Cl	1582 (m)	1563 (w)	*m*-CH_3	1599 (w)	1576 (w)
p-Br	1580 (m)	Shoulder	*o*-CH_3	1597 (vw)	1565 (vw)

1590 cm^{-1} presumably corresponds to the "1600 cm^{-1} aromatic vibration band", which is reported to occur within the range 1625–1575 cm^{-1} for most aromatic compounds (11). It was also found (cf. ref. 11) that the halogen-substituted benzene derivatives, particularly the iodo compounds, absorb near the lower limit of this range, while the locations of the absorptions of the nitro-substituted benzoyl chlorides occur at a frequency higher than average. Neither the location nor the intensity of the band appears to be quantitatively related to electronegativity, σ value, other electronic property, or to the size of the *o*-substituent. However, the more intense bands occur in the *p*- and *o*-isomers. Hence the band intensity may be related to mesomeric interaction.

The other infrared aromatic vibration band occurs in the 1600–1560 cm^{-1} region (cf. ref. 11). The data in Table III show that the band is more intense for *p*- and *o*-methoxybenzoyl chloride and this again indicates that mesomeric interaction enhances the band intensity. Moreover, the band appears to be weakest if mesomeric interaction is limited, as in nitrobenzoyl chlorides where both substituents are electron withdrawing, or as in *o*-toluoyl chloride where the methyl group could twist the chlorocarbonyl group out of the plane of the benzene ring and in this way inhibit mesomeric interaction. However, again neither band location nor band intensity could be quantitatively related to σ values or other electronic properties.

THE SPECTRA OF PARA-SUBSTITUTED BENZOYL CHLORIDES

The main ultraviolet absorption maxima of substituted benzoyl chlorides are listed in Table IV and are found to be essentially similar to the corresponding bands in *p*-substituted benzaldehydes and acetophenones (2, 3). This is further illustrated in Fig. 1, which shows the band similarity between a similarly *p*-substituted benzoyl chloride and benzaldehyde.

Since resonance forms of type I, sometimes favored by an electron-donating *p*-substituent, have previously been used to rationalize the observed spectral changes in *p*-substituted benzaldehydes (2) and acetophenones (3), these resonance forms can likewise rationalize the ultraviolet *B*-band spectral changes in *p*-substituted benzoyl chlorides. The wavelength displacements in *p*-substituted benzoyl chlorides relative to benzoyl chloride are, as expected, proportional to the wavelength displacements observed

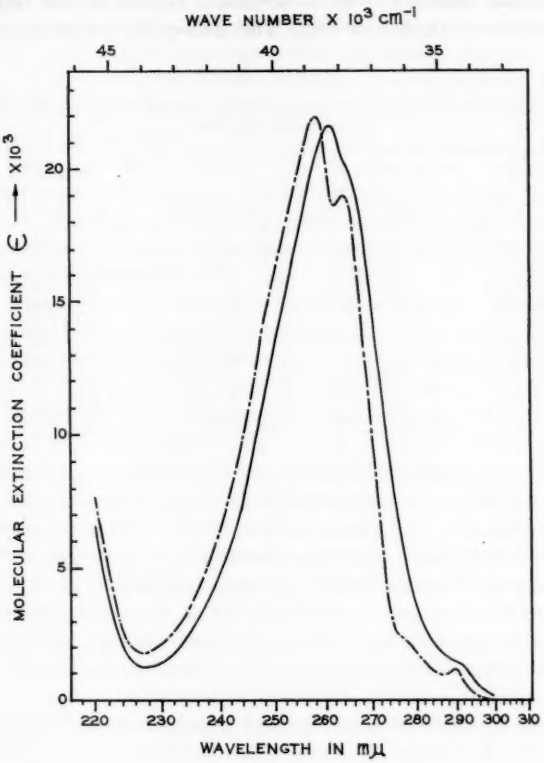


FIG. 1. The ultraviolet absorption spectra in cyclohexane solution of *p*-bromobenzoyl chloride (——) and *p*-bromobenzaldehyde (—·).

for *p*-substituted acetophenones, benzaldehydes, and nitrobenzenes relative to the non-*p*-substituted parent compounds. This is illustrated in Fig. 2, which uses the corresponding frequency displacements ($\Delta\nu$) instead of wavelength displacements ($\Delta\lambda$) (cf. ref. 2).

The slopes of the lines in Fig. 2 are in the order $-NO_2 >$ (—COCl) $>$ —CHO $>$ $-COCH_3$ (cf. also ref. 2). This order represents a measure of the different effects of a *p*-substituent on the various electron-withdrawing substituents (NO_2, COCl, etc.) when attached to the benzene ring. If it is assumed, as seems reasonable, that a substituent possessing a greater negative mesomeric effect can more effectively involve the electrons of an electron-donating *p*-substituent, the above order may also provide a measure of the negative mesomeric effect of the electron-withdrawing substituents. The order for the apparent mesomeric effect obtained in this way from Fig. 2 is as shown above (cf. also ref. 1 for the use of the term "apparent mesomeric effect"). Moreover, the maxima of the *B*-bands of nitrobenzene, benzoyl chloride, benzaldehyde, and acetophenone are located at 252, 242, 241, and 237.5 mμ respectively (see Table I and refs. 12, 2, and 3) and this also indicates increasing mesomeric interaction in the same order.

It may next be noted from the data listed in Table IV that the *B*-band of substituted benzoyl chlorides is again slightly unsymmetrical, with a shoulder usually occurring at

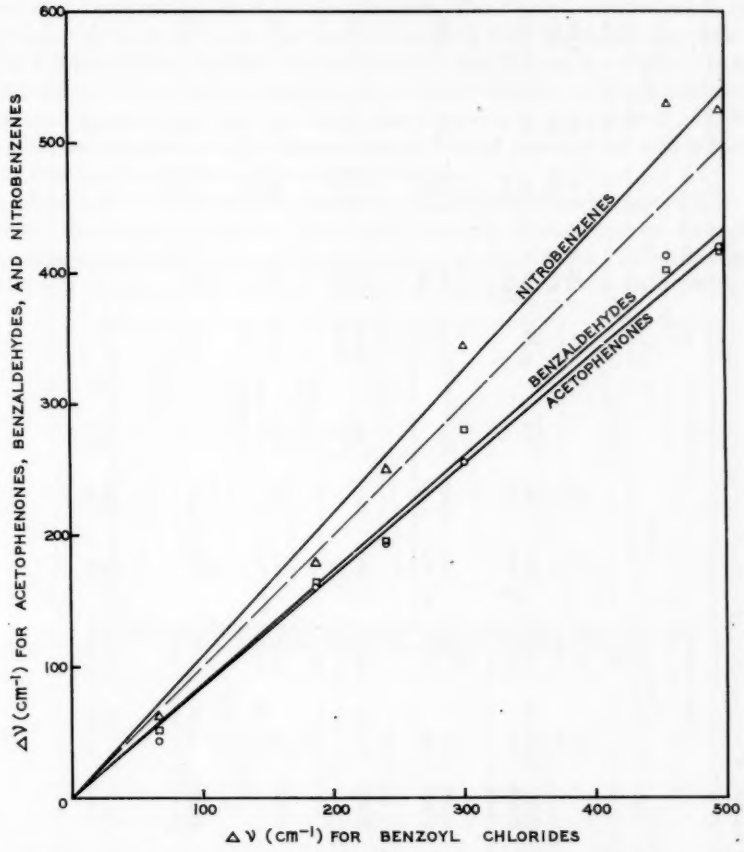


FIG. 2. Frequency displacements ($\Delta\nu$) in the *B*-band obtained on introducing para substituents in benzoyl chloride, benzaldehyde, acetophenone, and nitrobenzene (1, H; 2, F; 3, CH_3; 4, Cl; 5, Br; 6, MeO; and 7, I). Values (1 to 7 as $\Delta\nu$ increases) are for hexane solutions and are obtained from Table IV and from refs. 2, 3, and 12. △, nitrobenzenes; □, benzaldehydes; ○, acetophenones.

the longer wavelength side. Sometimes, as for the *p*-iodo- and *p*-methoxy-benzoyl chlorides the *B*-band occurs as a twin peak, but more frequently the second band occurs only as an ill-defined shoulder. The absence of this shoulder for the band at 255 mμ may also be taken as evidence to show that this band is not to be associated with benzoyl chloride but with nitrobenzene absorption.*

The ultraviolet spectra of *p*-substituted benzoyl chlorides also afford other bands in the 210–250 mμ region, which may either be *B*-bands, corresponding to locally excited states, or *A*-bands (for band nomenclature, see ref. 4). These bands are listed in Table IV,

**Further evidence that the band at 255 mμ in p-nitrobenzoyl chloride is a nitrobenzene B-band is provided by analogy with the spectrum of m-nitrobenzoyl chloride, which also shows an inflection near 255 mμ and, in addition, a band near 228 mμ (see Table IV). The m-isomer would be expected to show two B-bands, one more-intense B-band associated with benzoyl chloride absorption and one less-intense band associated with nitrobenzene absorption (13). The band at 228 mμ shows the characteristic shoulder associated with benzoyl chloride absorption and the inflection near 255 mμ in the m-isomer is therefore almost certainly a nitrobenzene B-band. This in turn suggests that the band at similar wavelength in the p-isomer is also a nitrobenzene B-band.*

TABLE IV

Main ultraviolet absorption maxima of ring-substituted benzoyl chlorides in cyclohexane solution

	Para isomer				Meta isomer						Ortho isomer					
	B-band		*C*-band		2nd *B*-band		*B*-band		*C*-band		2nd *B*-band		*B*-band		*C*-band	
Substituent	λ_{max} (mμ)	ϵ_{max}	λ_{max} (mμ)	ϵ_{max}	λ_{max} (mμ)	ϵ_{max}	λ_{max} (mμ)	ϵ_{max}	λ_{max} (mμ)	ϵ_{max}	λ_{max} (mμ)	ϵ_{max}	λ_{max} (mμ)	ϵ_{max}	λ_{max} (mμ)	ϵ_{max}
—F	246 *250*	14,500 *15,600*	*272*	*1,200*			240 248	13,500 12,000	288	2,200			237–238 *241*	13,000 *12,800*	286 294	2,200 1,800
—Cl	210–211 315 257 ca. *262*	12,000* 10,500* 21,000 *10,500*	ca. *289*	*1,100*	211 215	23,500 23,500	243 251	12,000 11,500	294 ca. *302*	1,600 *1,300*	212	20,500	244 *252*	9,000 *7,600*	292	1,700
—Br	211 218 261 ca. *264*	10,300* 8,000* 21,500 *20,000*	ca. *291*	*1,300*	214 217	24,000 23,600	244 252	11,000 11,000	296 ca. *305*	1,500 *1,100*	215	19,800	246 254	7,100 6,700	294	1,800
—I	227 245 275 285	7,000* 4,000* 18,000 17,500	—	—	230	29,500	ca. *244*	*10,000*	303	1,350	228 247	15,000 6,500*	255 264	6,000 4,400	304	2,200
—CH_3	210 214 253–254 *258*	10,600* 11,000* 18,000 *16,500*	ca. *279* ca. *290*	*2,000* *1,100*	211	15,000*	245 252–253	14,000 13,000	290	1,700	210	13,000	244 *252*	13,000 *12,000*	290	2,000
—OCH_3	217 224 272 280	12,000* 12,500* 19,500 19,200	—	—	219 222	23,000* 23,000	253 ca. *260*	10,000 *7,000*	312	3,100	214	19,500	ca. *244* 251	*8,500* 9,000	308	4,200
—NO_2	255	17,000	*290* *298* ca. *308*	*2,300* *2,100* *1,500*	ca. *247* ca. *258*	*10,500* *5,000*	228 ca. *233*	25,000 *22,500*	ca. *285* 297	*1,000* 950						

*B-band assignment doubtful.

the doubtful band assignments being indicated. The *B*-band assignment is favored if in the *m*-isomer there occurs a similar band, absorbing with increased absorption intensity, which is a *B*-band. For example, the bands at 211 and 215 mμ in *m*-chlorobenzoyl chloride are believed to correspond to chlorobenzene *B*-band absorption. Since reduced absorption maxima still occur at 211 and 215 mμ in the *p*-isomer, it is supposed that these maxima are also to be associated with chlorobenzene *B*-band absorption, which competes with *B*-band absorption involving the whole molecule.

The ultraviolet *C*-band affords the expected spectral changes (see ref. 3), that is, as mesomeric interaction increases, the *C*-band becomes less intense or disappears.

The infrared bands of the *p*-substituted benzoyl chlorides are listed in Tables II and III, and Fig. 3 shows the spectral tracings in the region 1550–1800 cm^{-1}. These data

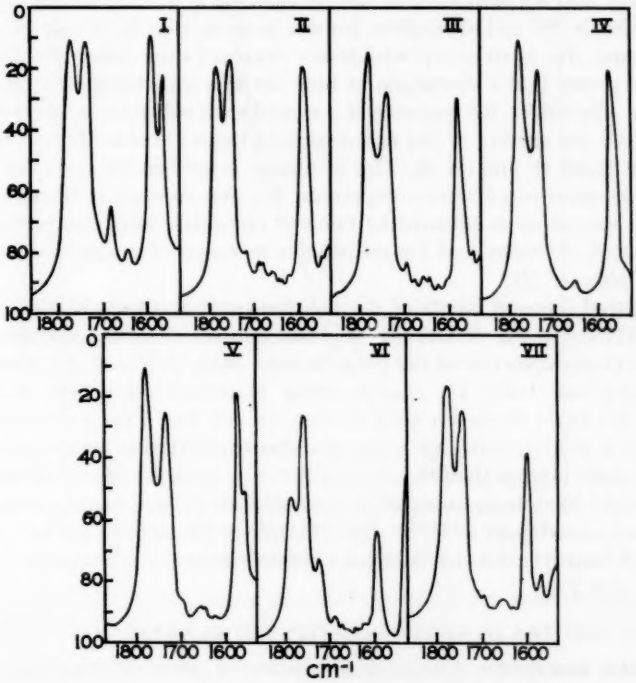


FIG. 3. The infrared bands (carbon tetrachloride solution) in the region 1550–1800 cm^{-1} of (I) *p*-methoxybenzoyl chloride, (II) *p*-fluorobenzoyl chloride, (III) *p*-chlorobenzoyl chloride, (IV) *p*-bromobenzoyl chloride, (V) *p*-iodobenzoyl chloride, (VI) *p*-nitrobenzoyl chloride, and (VII) *p*-toluoyl chloride.

show that the carbonyl band doublet occurs in all the *p*-substituted benzoyl chlorides investigated. Somewhat surprisingly, although carbonyl band frequencies of ring-substituted acetophenones showed a direct relationship with Hammett's σ values (14), no similar simple relationship is obtained between these σ values and either of the carbonyl band frequencies listed in Table II or with the arithmetic mean of the two carbonyl band frequencies. Plots of the carbonyl band frequencies against the functions σ^* and $(\sigma_p{}^- - \sigma')$, derived by Taft, Roberts, and Moreland (15), likewise all failed to show significant linearity. These observations point towards the possibility that in benzoyl chlorides an overtone or combination band occurs near the carbonyl band, and that the former bands,

because of a vibrational resonance effect, displace the carbonyl band from the position where it would otherwise have been expected to occur.

THE SPECTRA OF META-SUBSTITUTED BENZOYL CHLORIDES

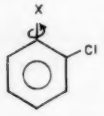
The ultraviolet spectra of *m*-substituted benzoyl chlorides frequently show two *B*-bands (cf. refs. 1, 2, and 12; for an explanation of this phenomenon in terms of molecular orbital theory, see ref. 16). One of these bands is associated with benzoyl chloride *B*-band absorption whereas the second *B*-band is associated with the other, non-benzoyl-chloride, monosubstituted benzene derivative. This latter *B*-band is designated in Table IV as the second *B*-band and it is usually the more intense band. This greater intensity may be related to the electron-withdrawing effect of the chlorocarbonyl group. Such an explanation may also account for the reverse relation in *m*-nitrobenzoyl chloride where the benzoyl chloride *B*-band absorption is more intense, that is, it may be assumed that this is so because the nitro group withdraws electrons even more effectively than the chlorocarbonyl group (for a discussion of how the spectral characteristics of one meta-substituent are affected by the presence of a second such substituent, see refs. 13 and 17).

As anticipated, the spectra of the *m*-substituted benzoyl chlorides and benzaldehydes are similar (see Table IV and ref. 2). This similarity is further illustrated in Fig. 4 for the spectra of the *m*-substituted nitro compounds. No new concept is therefore required to rationalize the spectra of *m*-substituted benzoyl chlorides, since the explanation of the spectra of benzoyl chlorides and benzaldehydes in terms of resonance forms of type I still holds (cf. also ref. 2).

The investigated infrared bands of the *m*-substituted benzoyl chlorides are shown in Tables II and III and in Fig. 5. The carbonyl bands again all show a doublet, even though for some of the compounds one of the peaks is only weak. A plot of the infrared carbonyl band frequencies (see Table II) against either Hammett's σ values or the functions σ^* or $(\sigma_m{}^-\sigma')$ (15) again showed a wide scatter (cf. ref. 14). Two additional points may be noted. First, in compounds such as *m*-chlorobenzoyl chloride, where one of the peaks is considerably more intense than the other, there is no evidence of any further band splitting such as might have been expected if the molecule existed in two *s*-cis, *s*-trans conformations which absorb maximally at slightly different frequencies (cf. ref. 14). Secondly, in *m*-substituted benzoyl chlorides the peak at lower frequency is frequently more intense (cf. Figs. 3, 5, and 7).

THE SPECTRA OF ORTHO-SUBSTITUTED BENZOYL CHLORIDES

The ultraviolet absorption spectra of *o*-substituted benzoyl chlorides, like those of the corresponding *m*-isomers, again generally exhibit two *B*-bands. Steric interactions in compounds such as *o*-substituted benzoyl chlorides would be expected to cause intensity



(II)

X = CHO, $COCH_3$, COCl, or NO_2

decreases in the *B*-band compared with the intensities in the *m*-isomers, and such intensity decreases are in fact observed (see Table IV). This is further illustrated in Fig. 6 for *o*-chlorobenzoyl chloride (II, X = COCl).

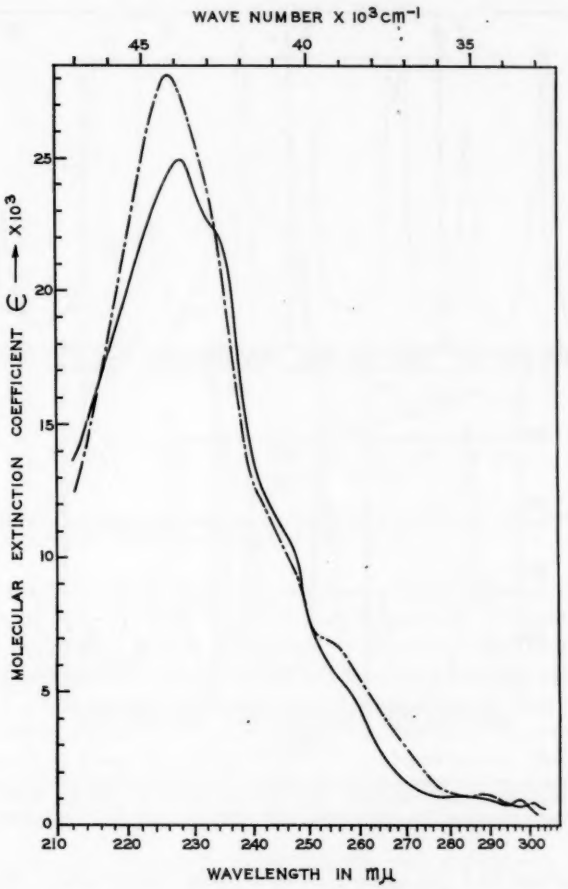


FIG. 4. The ultraviolet absorption spectra in cyclohexane solution of *m*-nitrobenzoyl chloride (——) and *m*-nitrobenzaldehyde (—·).

Figure 6 shows that the *B*-band of *o*-chlorobenzoyl chloride is less intense than that of the *m*-isomer, and further, that the *B*-bands of *o*-chlorobenzoyl chloride and *o*-chlorobenzaldehyde are again similar but that the former *B*-band is also less intense than the *B*-band in *o*-chlorobenzaldehyde. If it is assumed that in *o*-chlorobenzoyl chloride steric interactions predominantly affect the molecule by twisting the group X out of the plane of the benzene ring (as indicated in structure II), the intensities of the *B*-bands associated with the PhX chromophores can be taken as a semiquantitative measure of the steric interactions (cf. ref. 18). The relevant absorptivities of both *o*- and *m*-isomers as well as the ratio of the absorptivities of the two *B*-bands for compounds II (X = —CHO, —COCl, —$COCH_3$, and —NO_2) are listed in Table V. The absorptivity ratios, thus obtained, are in the order —NO_2 > —$COCH_3$ > —COCl > —CHO and this order may be taken as a measure of the effective interference radii of these substituents. Other factors may also affect the absorptivity ratios. For example, the different compounds II

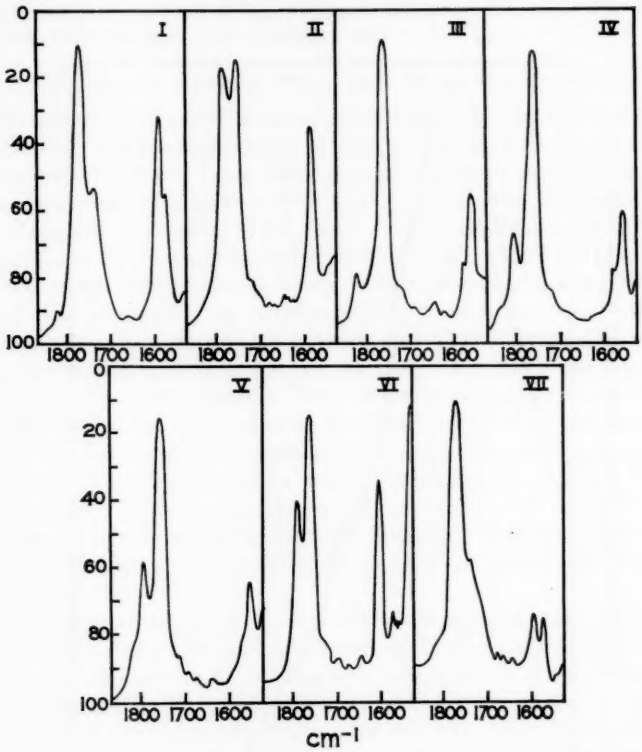


FIG. 5. The infrared bands (carbon tetrachloride solution) in the region 1550–1800 cm^{-1} of (I) *m*-methoxybenzoyl chloride, (II) *m*-fluorobenzoyl chloride, (III) *m*-chlorobenzoyl chloride, (IV) *m*-bromobenzoyl chloride, (V) *m*-iodobenzoyl chloride, (VI) *m*-nitrobenzoyl chloride, and (VII) *m*-toluoyl chloride.

may not all exist in one and the same *s*-cis or *s*-trans conformation. However, orders for the effective interference radii similar to those deduced from the chloro-substituted compounds can be obtained from the absorptivity ratios of the corresponding *o*-bromo, *o*-iodo, *o*-methoxy, and *o*-nitro compounds, and this increases our confidence in the proposed order.

TABLE V

Absorptivity values (ϵ_{max}) of the *B*-band associated with the chromophoric system PhX in compound II*

	X in compound II:			
	CHO†	COCl‡	$COCH_3$§	NO_2‖
Compound II (*o*-isomer)	11,000	9,000	5,700	4,000
m-Isomer of compound II	11,500	12,000	10,000	7,800
ϵ_{max} ratio of *m*-isomer/*o*-isomer	1.05	1.33	1.75	1.95

*Values in cyclohexane solution unless otherwise stated.
†Values from ref. 2.
‡This paper.
§Values from ref. 3.
‖Values in 95% aqueous ethanol; see ref. 19.

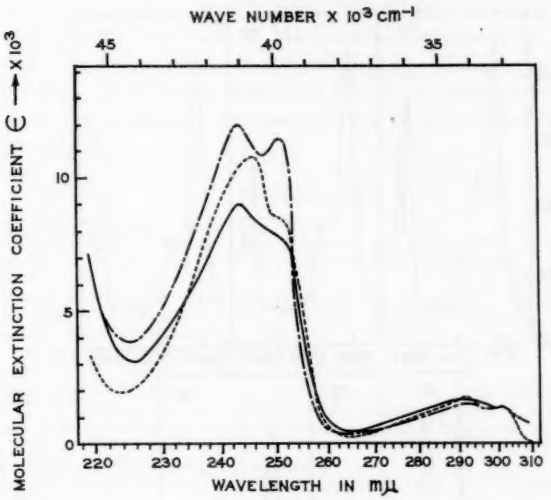


FIG. 6. The ultraviolet absorption spectra in cyclohexane solution of *o*-chlorobenzoyl chloride (——), *m*-chlorobenzoyl chloride (—·), and *o*-chlorobenzaldehyde (– –).

The ultraviolet *C*-bands of both *m*- and *o*-substituted benzoyl chlorides exhibit the usual changes (cf. ref. 3), that is, the C-bands generally become progressively more pronounced in the order *p*-isomer < *m*-isomer < *o*-isomer (see Table IV).

The investigated infrared bands of the *o*-substituted benzoyl chlorides are shown in Tables II and III and in Fig. 7. The carbonyl bands again all show a doublet, but as in the *m*-isomers one of the peaks is usually weaker. However, in the *o*-isomer the less-intense band is the band at *lower* frequency, whereas in the *m*-isomer the less-intense band is usually the band at *higher* frequency. In the *p*-isomer the two bands seem to be generally of similar intensity (see Table II, and cf. Figs. 3, 5, and 7).

SOME CONCLUDING REMARKS CONCERNING THE CARBONYL BAND DOUBLET IN BENZOYL CHLORIDES

The origin of the doublet in the infrared carbonyl band is not clear. One explanation is that the band occurs because of Fermi resonance between the carbonyl vibration and a close-lying overtone. In fact, benzoyl chloride shows an intense band at 875 cm^{-1} and doubling this frequency would place the overtone at 1750 cm^{-1}—reasonably close to the observed "carbonyl bands" at 1782 and 1740 cm^{-1} (see Table II). Hence it is possible that an anharmonicity effect brings the two vibrations sufficiently close together to cause the observed doublet (cf. ref. 20 for an explanation on these lines to account for the carbonyl band doublet in cyclopentanone). Likewise an overtone near 1740 cm^{-1} of the band at 870 cm^{-1} in *p*-toluoyl chloride can account for the doublet at 1777 and 1744 cm^{-1}. Similar explanations could hold for other benzoyl chlorides. Sometimes, the overtone of the band near 850 cm^{-1} is not sufficiently close to account satisfactorily for the doublet. For example, in *m*-nitrobenzoyl chloride the doublet occurs at 1792 and 1764 cm^{-1} and the overtone would be expected to occur near 1690 cm^{-1} (2×845 cm^{-1}). However, there are other bands (for example, *m*-nitrobenzoyl chloride affords a band at 925 cm^{-1}), overtones of which could also account for the observed doublets. Moreover,

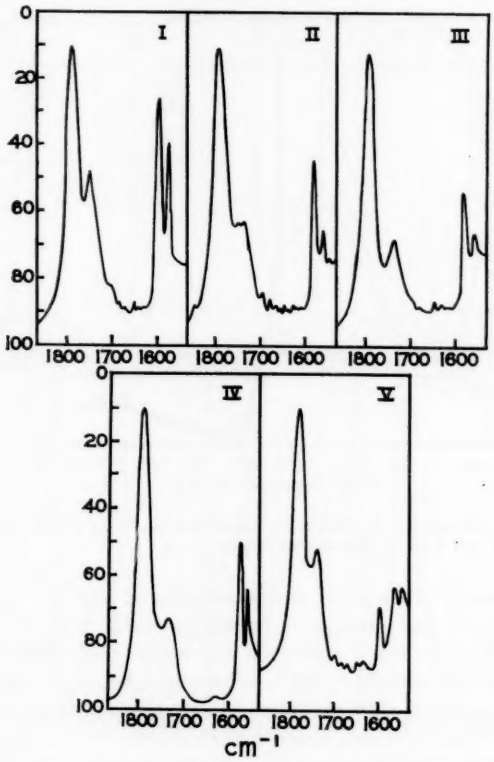


FIG. 7. The infrared bands (carbon tetrachloride solution) in the region 1550–1800 cm^{-1} of (I) *o*-methoxybenzoyl chloride. (II) *o*-chlorobenzoyl chloride, (III) *o*-bromobenzoyl chloride, (IV) *o*-iodobenzoyl chloride, and (V) *o*-toluoyl chloride.

it is also possible to postulate a combination band (cf. ref. 21) which may account for the observed doublet.

This type of explanation is probably the best that can be put forward, but it is not entirely satisfactory. Thus it accounts for the doublet in what is, at best, a semiquantitative manner. For example, in *p*-fluorobenzoyl chloride the overtone of the band at 880 cm^{-1} is expected to occur near 1760 cm^{-1} and this would be anticipated to lead to a *weak* band on the low-frequency side of the carbonyl band at 1786 cm^{-1}. However, the peak at lower frequency (at 1754 cm^{-1}) is *more intense*, although for most other benzoyl chlorides there is the expected reverse relation, that is, the peak on the overtone side is less intense. Moreover, the unusual absence of any direct relationship between either of the carbonyl band frequencies or their means and Hammett's σ values suggests that the original carbonyl frequency is appreciably modified.

Other explanations, such as involvement of intermolecular interactions, or the existence of different conformational isomers in equilibrium, are even more unsatisfactory. Consequently, in the absence of any other more satisfactory explanation, the most probable explanation is that the doublet occurs because of an intermolecular vibration. The understanding of the precise mechanism of this vibration clearly requires further study.

ACKNOWLEDGMENTS

The authors are greatly indebted to Miss Ingrid Baumann for competent technical assistance in preparing the compounds studied and in determining the ultraviolet data. Thanks are also due to Mr. D. L. Coffen and Mr. A. A. Sioumis for determining the infrared spectra, and the financial assistance of the National Research Council is again gratefully acknowledged.

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THE REACTION OF ETHANOL VAPOR WITH Hg 6($^3P_1$) ATOMS[1]

ARTHUR R. KNIGHT AND HARRY E. GUNNING

ABSTRACT

The reaction of ethanol vapor with Hg 6($^3P_1$) atoms has been investigated under static conditions at 25° C. To determine the nature and efficiency of the primary process, the reaction has been studied in the presence of nitric oxide, and also under conditions of intermittent illumination. For the pure substrate the volatile products were H_2 (0.53), CH_3CHO (0.08), CO (0.025), C_2H_6 (0.006), and CH_4 (0.002), with the bracketed numbers representing the quantum yields at zero exposure time. The heavy product was a mixture of butanediols containing 90% 2,3-, 8% 1,3-, and 2% 1,4-butanediol. With 20% added NO, the products were EtONO (0.25), N_2O (0.14), H_2O, and H_2 (0.017). Under intermittent illumination, the quantum yield (Φ) of H_2 formation for pure substrate was measured as a function of the light period (t_L) and the dark period (t_D). For maximum values of $\Phi(H_2)$, it was found that t_D had to exceed ca. 120 msec. Under these conditions, $\Phi(H_2)$ rose linearly with decreasing log t_L to a maximum value of 0.96 at t_L less than 0.4 msec.

From the study it is concluded that ethanol reacts with Hg 6($^3P_1$) atoms to form ethoxy radicals and H atoms with at least 96% efficiency. The primary ethoxy radicals disappear by hydrogen abstraction from the substrate to form mainly CH_3CHOH radicals. Under continuous illumination the low value (0.53) for $\Phi(H_2)$ is caused principally by the addition of H atoms to the CH_3CHOH radicals.

INTRODUCTION

Recent studies (1, 2) have shown that the primary reaction between methanol vapor and Hg 6($^3P_1$) atoms leads almost exclusively to the formation of CH_3O and H. In addition, by the use of special intermittent-illumination techniques, it has been found in this laboratory (3) that the primary quantum yield (Φ) for H-atom formation is at least 0.89, and likely unity. Thus, with a light period (t_L) of 0.156 msec and a dark period (t_D) of 160 msec, $\Phi(H_2)$ was 0.89; whereas, under steady illumination, $\Phi(H_2)$ was only 0.46 when extrapolated to its maximum value at zero extent of reaction (2, 3). The low value of $\Phi(H_2)$ under steady illumination was ascribed mainly (3) to the combination of H with CH_2OH.

If O—H bond scission is a general characteristic of the primary reaction of Hg 6($^3P_1$) atoms with the alcohols, these substrates could provide convenient sources for studying the properties of alkoxy radicals.

The ethanol reaction was the subject of an early investigation by Bates and Taylor (4). In the present study the decomposition has been examined under both continuous and intermittent illumination. Emphasis has been placed on the nature and efficiency of the primary process.

The details of the investigation follow.

EXPERIMENTAL

For the static runs at 25°, under continuous illumination, the apparatus was essentially identical with that used for the methanol reaction (2). The single- and double-sector equipment used for the intermittent-illumination studies has also been described previously (3). Light intensities, at 2537 Å, were determined as before (3) by propane actinometry (5, 6).

Benzene-free ethanol, 99.9% pure, was degassed, trap-to-trap distilled, and the middle fraction used without further purification.

[1]*Manuscript received July 27, 1961.*
Contribution from the Department of Chemistry, University of Alberta, Edmonton, Alberta. A portion of this paper was presented at the 139th Meeting of the American Chemical Society, St. Louis, Missouri, March, 1961.

Analysis of the condensable products, excluding the glycols, was done by G.L.P.C. with "Ucon" and "Apiezon L" columns as previously described (2). Identification by retention time for each condensable product, except the glycols, was confirmed by mass spectrometry. The moles of product, non-condensable in liquid nitrogen, were determined from the PV/RT ratio in a calibrated gas burette. By mass spectrometry this product was shown to contain H_2, CO, and CH_4. The mole fractions of CO and CH_4 in the product were determined by G.L.P.C., on a 30/60-mesh molecular-sieves column, operating at room temperature, with H_2 carrier at a flow rate of 50 cc/minute.

The high-boiling glycol products were determined by dissolving the cell deposit in acetone, and analyzing this solution by G.L.P.C. The glass column used was 2.5 m in length, with 6 mm O.D., and filled with 15 wt-% didecyl phthalate on Celite. The column was operated at 120° with the flow rate of the H_2 carrier at 70 cc/minute. The katharometer was maintained at 150° and a current of 300 ma. A series of calibrations were performed with authentic samples of the three butanediols at various concentrations in acetone. The relative detector responses for the three glycols were found to depend slightly upon concentration. Correction was made in each case for this concentration effect. For each heavy-product analysis, the ratio of glycol to solvent was determined, and the appropriate relative responses were employed in the calculation of the percentage yields.

RESULTS

The runs with pure ethanol, under steady illumination, were carried out at a substrate pressure of 40 mm. The absorbed light intensity (I_a) was 1.60 ± 0.03 μeinsteins/minute. During the reaction the heavy product was observed to form in fine droplets, largely on the incident face of the cell.

The volatile products of the reaction were H_2, CH_3CHO, CO, C_2H_6, and CH_4, in order of decreasing importance. From Fig. 1, it is seen that $\Phi(H_2)$ rises with decreasing duration of exposure (t). By a short extrapolation, $\Phi^0(H_2) = 0.53$. The Φ's for CH_3CHO and C_2H_6 are shown in Fig. 2, as a function of t. $\Phi(CH_3CHO)$ falls rapidly with increasing t, indicating consumption by secondary reaction; whereas $\Phi(C_2H_6)$ is invariant in t. We find $\Phi^0(CH_3CHO) = 0.08$ and $\Phi^0(C_2H_6) = 0.006$. From Fig. 3, $\Phi(CH_4)$ rises linearly with t from $\Phi^0(CH_4) = 0.002$. $\Phi(CO)$ also rises with t, approaching a constant value of ca. 0.05. For $\Phi^0(CO)$ we find 0.025.

Long runs were required to obtain sufficient yields of the heavy product for total analysis. For runs with $t = 3$ and 6 hours, the heavy product was found to contain at least 85–90% of 2,3-butanediol. Complete analyses were performed on three separate runs with $t = 10$ hours. The composition of the heavy product was: 90% 2,3-butanediol, 8% 1,3-butanediol, and 2% 1,4-butanediol.

For the study of the reaction in the presence of nitric oxide, a mixture of 40 mm of EtOH and 10 mm of NO was used. The products were found to be EtONO, N_2O, H_2O, and H_2. No quantitative analysis was made for the water product. It should be noted that CH_3CHO was not detected in the reaction, whereas in the CH_3OH—NO system, HCHO was a minor but significant product (2). In Fig. 4, Φ(EtONO) is shown as a function of t. In order to correct the yield for competitive quenching by NO, the quenching cross section for EtOH was taken as 9 Å^2. The resulting quenching correction factor was 1.7. From Fig. 4, it is apparent that ethyl nitrite is being decomposed in secondary reaction. For Φ^0(EtONO) we obtain 0.25. Figure 5 shows the behavior of $\Phi(H_2)$ and $\Phi(N_2O)$ for the inhibited reaction. There is a gradual rise in $\Phi(N_2O)$ with decreasing t;

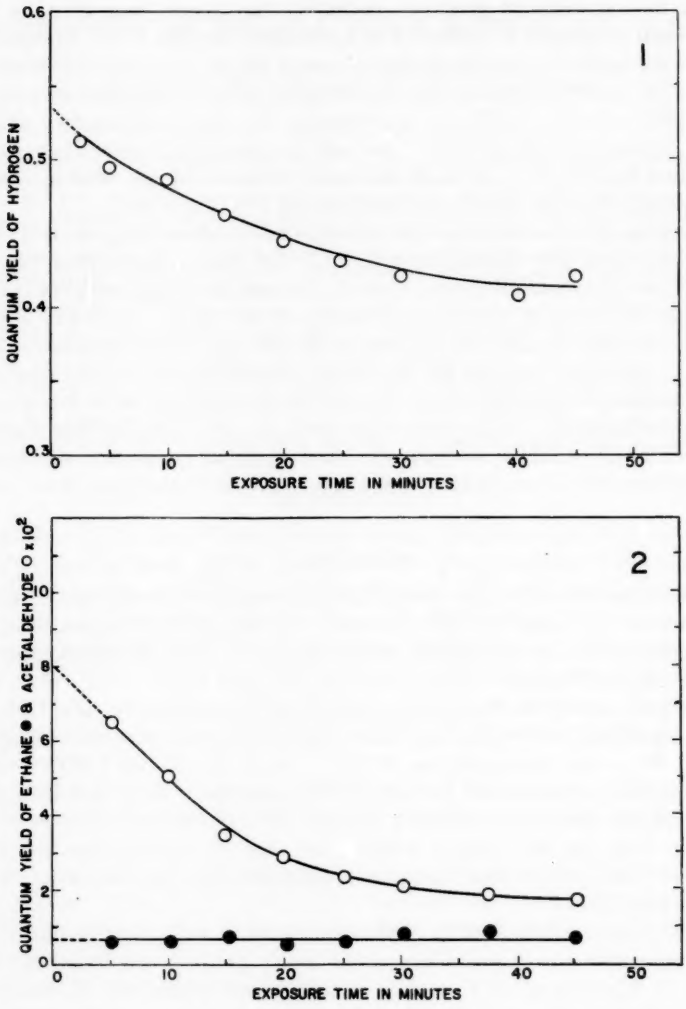

FIG. 1. $\Phi(H_2)$ vs. t for ethanol vapor at a pressure of 40 mm.
FIG. 2. $\Phi(C_2H_6)$, ●, and $\Phi(CH_3CHO)$, ○, vs. t for ethanol vapor at a pressure of 40 mm.

whereas $\Phi(H_2)$ is invariant in t. Extrapolation gives $\Phi^0(N_2O) = 0.14$, and $\Phi^0(H_2) = \Phi(H_2) = 0.017$.

In the intermittent-illumination studies, $\Phi(H_2)$ was determined as a function of both t_L and t_D. In all runs, pure substrate was used at a pressure of 40 mm. In order to assess the influence of t_D on $\Phi(H_2)$ at constant t_L, a series of runs were done with $t_L = 2.04$ msec, and t_D varying from 22.7 to 148 msec. For these runs, I_a values of 1.30, 1.43, and 1.60 μeinsteins/minute were used. The net duration of exposure in all cases was under 5 minutes. There was no dependence of $\Phi(H_2)$ on t under these conditions. The plot of $\Phi(H_2)$ vs. t_D is shown in Fig. 6. With increasing t_D, $\Phi(H_2)$ rises sigmoidally from 0.58

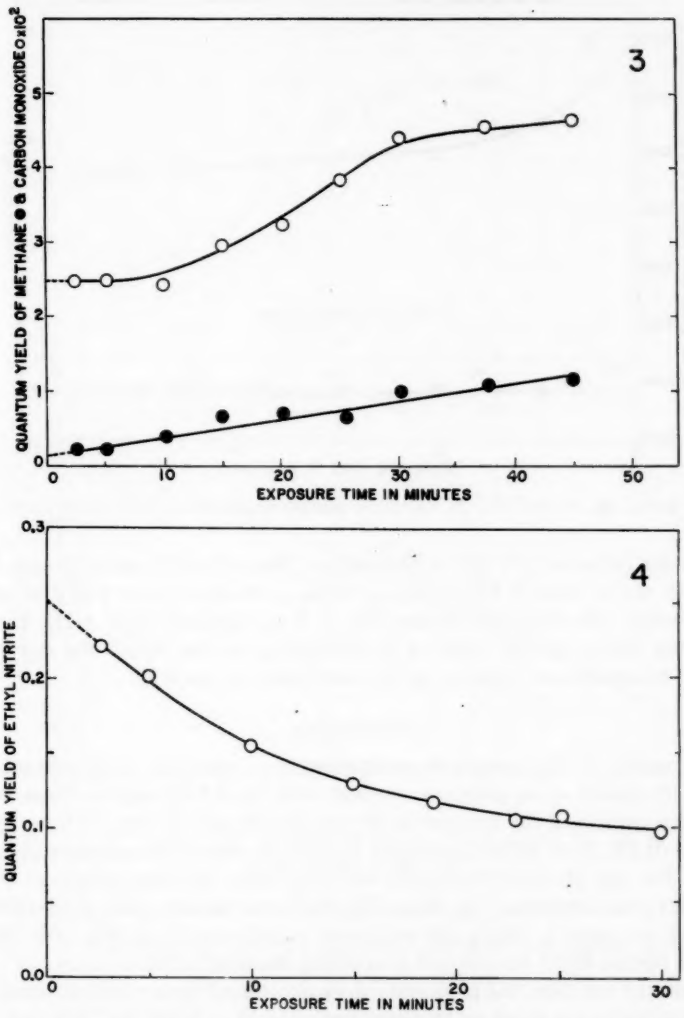

FIG. 3. $\Phi(CH_4)$, ●, and $\Phi(CO)$, ○, vs. t for ethanol vapor at a pressure of 40 mm.
FIG. 4. $\Phi(EtONO)$ vs. t for a mixture of 40 mm of ethanol and 10 mm of nitric oxide.

at t_D = 22.7 msec, to 0.76 at t_D = 148 msec. The value of $\Phi(H_2)$ becomes independent of t_D for t_D ca. 120 msec.

The relation between $\Phi(H_2)$ and t_L is shown in Fig. 7, using a logarithmic abscissa. Two separate series of runs are shown on the same curve. For t_L in the range 0.835 to 5.09 msec, the single sector was used with t_D at 103 msec. The I_a values were 0.72 and 1.43 μeinsteins/minute, and the net durations of exposure were in the range 1.00 to 5.00 minutes. For t_L values between 0.125 and 0.589 msec, the double sector was employed, with t_D at 160 msec. For these runs, I_a was 1.25 μeinsteins/minute, and the net durations

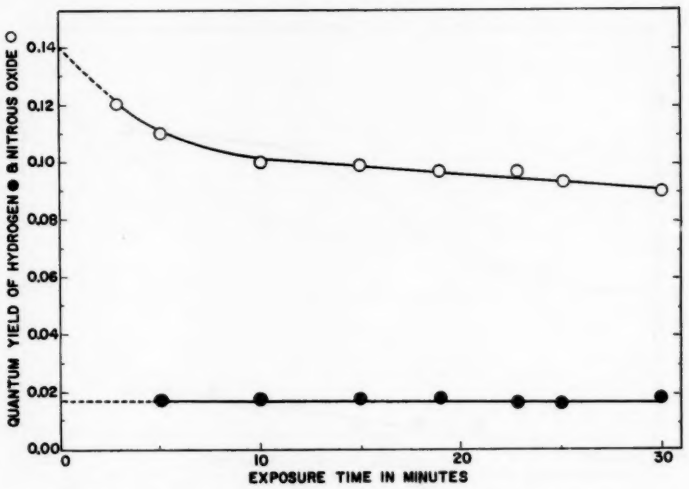

FIG. 5. $\Phi(H_2)$, ●, and $\Phi(N_2O)$, ○, vs. t for a mixture of ethanol and 10 mm of nitric oxide.

of exposure were between 0.77 and 1.08 minutes. Since the two series of runs fall on the same curve, as can be seen in Fig. 7, this is taken as evidence that $\Phi(H_2)$ is independent of t_D in the region 103–160 msec. From Fig. 7, it is apparent that $\Phi(H_2)$ rises linearly with decreasing log t_L to a t_L value of ca. 0.4 msec, beyond which the curve begins to flatten out. The maximum value of $\Phi(H_2)$ was found to be 0.96.

DISCUSSION

From the results of the present investigation, it is apparent that ethanol resembles methanol (1, 2) closely in its primary reaction with Hg $6(^3P_1)$ atoms. Thus, considering first the decomposition of the mixture of 40 mm EtOH and 10 mm NO, we find as products EtONO (0.25), N_2O (0.14), H_2O, and H_2 (0.017), where the numbers in parentheses give the Φ^0's. For the MeOH–NO system with the same NO concentration, Φ(MeONO) was 0.20 with t = 5.0 minutes (2). From Fig. 4, it can be seen that Φ(EtONO) has the same value at the same t. Again for methanol containing 10 mole% NO, $\Phi^0(H_2)$ was 0.012, and we obtain 0.017 for ethanol containing 20 mole% NO.

For the inhibited reaction, the products can be accounted for by the following sequence:

$$CH_3CH_2OH + Hg^* \rightarrow CH_3CH_2O + H + Hg, \quad [1]$$

$$CH_3CH_2O + NO \rightarrow CH_3CH_2ONO, \quad [2]$$

$$H + NO \rightarrow HNO, \quad [3]$$

$$HNO + HNO \rightarrow H_2O + N_2O, \quad [4]$$

$$HNO + HNO \rightarrow 2NO + H_2. \quad [5]$$

For reaction [2], Gray and Williams (7) estimate an exothermicity of 35–40 kcal/mole. Levy (8) has shown that [2] occurs in the thermolysis of Et_2O_2 in the presence of NO, and in the decomposition of ethyl nitrite (8) and ethyl nitrate (9). There is also some evidence (8, 10) that in the photolysis of Et_2O_2–NO mixtures, ethyl nitrite forms by [2].

In the above sequence, reactions [3], [4], and [5] have been discussed previously (2).

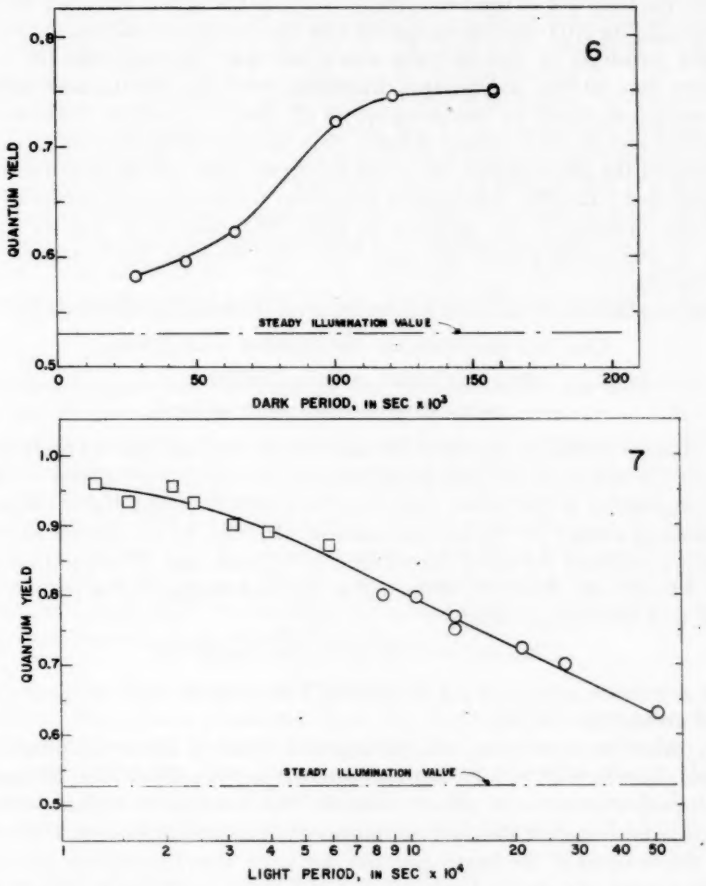

FIG. 6. $\Phi(H_2)$ as a function of dark period, for a constant light period of 2.04 msec, for ethanol vapor at a pressure of 40 mm.

FIG. 7. $\Phi(H_2)$ as a function of the logarithm of the light period, for dark periods of 103 msec, ○, and 160 msec, □, for ethanol vapor at a pressure of 40 mm.

From the ratio $\Phi^0(N_2O)/\Phi^0(H_2)$, k_4/k_5 is estimated to be ca. 8. To explain the fact that Φ^0(EtONO) is only 0.25, we suggest the reaction

$$CH_3CH_2O + HNO \rightarrow CH_3CH_2OH + NO. \qquad [6]$$

Since D(EtO–H) is 99 kcal/mole (7), step [6] should be highly exothermic. The fact that CH_3CHO was not detected as a product would suggest that there is no abstractive attack of ethoxy radicals on the ethyl nitrite. Here it is pertinent to note that Levy found that both ethyl nitrite (8) and ethyl nitrate (9) are relatively inert to ethoxy radicals at 181°. In the previous study (2), on the CH_3OH–NO reaction, HCHO was shown to be a minor secondary product which increased in importance with the exposure time. On energetic grounds, one would expect that EtO radicals would similarly remove a secondary hydrogen from EtONO, leading to the formation of CH_3CHO as a product. In our opinion, the

difference in the behavior of the two systems is due to the higher efficiency of the association reaction, [2], for EtO radicals compared with the analogous reaction for MeO radicals. Thus in the pyrolysis of MeONO the first-order rate constant falls off at substrate pressures less than 50 mm, indicating a dreierstoss restriction on the association reaction (7). This restriction should be less stringent for [2]. Hence it is likely that the stationary-state concentration of EtO radicals is lower than that for MeO radicals at the same NO concentration in the two systems. Since the aldehyde yield will be proportional to (RO), it is probable that CH_3CHO is formed in quantities too small for detection by our analytical methods. Presumably the decrease in Φ(EtONO) with t (cf. Fig. 4) is due to the photolysis of this product into EtO and NO. The resulting EtO radicals could then disappear by [6].

In the decomposition of the pure substrate, step [1] would be followed by:

$$CH_3CH_2O + CH_3CH_2OH \rightarrow CH_3CH_2OH + CH_3CHOH, \quad [7]$$

$$H + CH_3CH_2OH \rightarrow H_2 + CH_3CHOH, \quad [8]$$

$$2(CH_3CHOH) \rightarrow CH_3CHOHCHOHCH_3. \quad [9]$$

From the relative yields of the three butanediols, it follows that CH_2CH_2OH radicals must also be formed in [7] and [8], by abstraction at the methyl group of the ethanol. From the composition of the heavy product, $(CH_3CHOH)/(CH_2CH_2OH)$ must be ca. 11.

The activation energy for [7] has not been determined. If we assume that the C—H bond energy in ethanol does not exceed that in ethane, step [7] should be exothermic to at least 3 kcal/mole. Recently Wijnen (11) has reinvestigated the photolysis of ethyl propionate, and for the reaction

$$CH_3CH_2O + EtCOOEt \rightarrow CH_3CH_2OH + R \quad [10]$$

he finds an activation energy of 5.5 kcal/mole. It is unlikely that the activation energy of [7] would exceed that of [10].

The only other product in the ethanol reaction which is clearly of primary origin is acetaldehyde, for which $\Phi^0 = 0.08$. In this system, it seems unlikely that the acetaldehyde arises by disproportionation of ethoxy radicals. The absence of hydroxy-ethers among the products would suggest that the stationary-state concentration of EtO is very low. Now from the analysis of the heavy fraction, we know that the radicals (R) undergoing combination consist of a ca. 11:1 mixture of CH_3CHOH and CH_2CH_2OH. If the disproportionation of the R radicals is the source of the acetaldehyde, the dominant reaction would be:

$$CH_3CHOH + CH_3CHOH \rightarrow CH_3CH_2OH + CH_3CHO. \quad [11]$$

This reaction would involve an intermediate $\dot{C}H_2CHOH$ structure, which should rearrange readily to CH_3CHO. Since $\Phi^0(H_2) = 0.53$, Φ(R) must have the same value. Thus k_{11}/k_9 would be $(0.08)/(0.26_5-0.08)$, or ca. 0.3. This value is likely low, since, as will be seen, CH_3CHO is suffering decomposition by secondary reaction.

The rapid decrease in $\Phi(CH_3CHO)$ with t is evident from Fig. 2. Since the weakest C—H bond in CH_3CHO is 80 kcal/mole (7), the reaction

$$R + CH_3CHO \rightarrow RH + CH_3CO \quad [12]$$

will be highly exothermic, and the one likely to be responsible for CH_3CHO consumption. From our data, the mean rate of CH_3CHO formation during the first 5 minutes of reaction is 0.10_4 μmoles/minute. With no secondary destruction of this product, there should be $45\times0.10_4$ or 4.7 μmoles at $t = 45$ minutes. Since only 1.2 μmoles were found at $t = 45$ minutes, 3.5 μmoles have been consumed. The yield of CO at $t = 45$ minutes was 3.3

μmoles. We are, of course, assuming that the CO arises from the decomposition of the CH_3CO radicals formed in [12]. The accountability in CH_3 is not quite so satisfactory. At $t = 45$ minutes, there were 1.1 μmoles of CH_4 and 0.45 μmoles of C_2H_6. We can therefore account for 2.0 of the 3.3 μmoles of CH_3 in this manner.[2]

From the results of the studies under intermittent illumination, as shown in Fig. 7, we can now say that the primary quenching reaction [1] is at least 96% efficient. Furthermore, since in the inhibited reaction there is no evidence of any other radical association product than ethyl nitrite, it appears justifiable to say that $\Phi(H) = \Phi(CH_3CH_2O) = 0.96$. Since the effect of intermittent illumination has been discussed in some detail for the methanol reaction (3), we will limit ourselves here to the conclusion that the low $\Phi(H_2)$ under steady illumination is due mainly to substrate re-formation by the addition of H atoms to the radicals present in the system. For ethanol the dominant reaction would be:

$$H + CH_3CHOH \rightarrow CH_3CH_2OH. \qquad [13]$$

The main difference between methanol (3) and ethanol is that the $\Phi(H_2)$ for the latter rises more rapidly toward unity with decreasing t_L. Now at the same I_a and primary quantum efficiency, the reactions controlling the H-atom concentration will be [8] and [13] and their analogues for methanol. An obvious conclusion is that the abstraction reaction [8] is faster for ethanol than methanol, which would result in a lower value for (H) in the ethanol system, and a reduced rate of substrate re-formation by [13]. For both methanol (3) and ethanol (Fig. 6), it was necessary for t_D to be at least 100 msec to obtain the maximum value of $\Phi(H_2)$ at a given t_L. It seems reasonable to conclude that the t_D value of 100 msec represents the minimum time required for the radical concentration to decay to zero between successive light pulses.

CONCLUSIONS

As a result of the present investigation, it can be concluded that ethanol molecules react with Hg $6(^3P_1)$ atoms by O—H bond scission to form ethoxy radicals and H atoms with at least 96% efficiency. The ethoxy radicals and H atoms react with the substrate by abstraction to form mainly CH_3CHOH radicals. The low value for $\Phi(H_2)$ under continuous illumination is due largely to the addition of H atoms to CH_3CHOH radicals.

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[2]*We are indebted to the reviewer of this paper for pointing out that the accountability in* CH_3 *could be improved by considering that some* CH_3 *will disappear by combination with* CH_3CHOH *to form isopropyl alcohol. A small yield of this compound would not have been detected in our G.L.P.C. analysis. Pertinently, small yields of* CH_3CH_2OH *were found in the previous study on* CH_3OH *(2).*

CONFIGURATION OF GLYCOSIDIC LINKAGES IN OLIGOSACCHARIDES

IX. SYNTHESIS OF α- AND β-D-MANNOPYRANOSYL DISACCHARIDES[1]

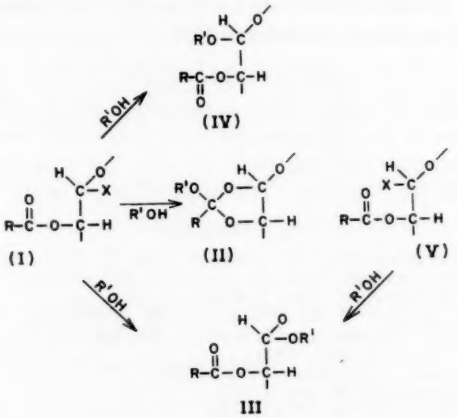
P. A. J. GORIN AND A. S. PERLIN

ABSTRACT

The Königs–Knorr condensation of 4,6-di-*O*-acetyl-2,3-*O*-carbonyl-α-D-mannopyranosyl bromide with 1,2,3,4-tetra-*O*-acetyl-β-D-glucose provides a synthetic route to 6-*O*-β-D-mannopyranosyl-D-glucose. When some other derivatives of α-D-mannopyranosyl bromide—the 2,3,4,6-tetra-*O*-benzoyl-, 3,4,6-tri-*O*-acetyl-, or 3,4,6-tri-*O*-acetyl-2-*O*-benzyl derivative—are used as the halide component the α-D-linked isomer of this disaccharide is produced. The steric outcome of Königs–Knorr syntheses involving these and other derivatives of α-D-mannopyranosyl bromide is discussed in terms of the influence of neighboring groups, and of conformational and solvent effects.

Lead tetraacetate oxidation of 6-*O*-β-D-mannopyranosyl-D-glucose, followed by reduction, affords 4-*O*-β-D-mannopyranosyl-D-erythritol, a metabolite produced by *Ustilago* species (PRL 627).

In an earlier study (1) it was found that the major disaccharides produced by the Königs–Knorr condensation of 2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyl bromide with 1,2,3,4-tetra-*O*-acetyl-β-D-glucose and -mannose possess the α-D-, rather than the β-D-linkage assigned originally (2). This finding was consistent with current views (3–7) on the reactions of acylated glycosyl halides with alcohols, according to which a 1,2-*trans*-halide (I, R = CH_3 or phenyl) due to participation of the 2-acyloxy group, is expected to yield either an orthoester (II) or the 1,2-*trans*-glycoside (III), although a small amount of inversion may also occur to yield the 1,2-*cis*-glycoside (IV). Predominant inversion would be expected with the 1,2-*cis*-halide (V), the *trans*-glycoside again being formed. In several instances, however, 1,2-*cis*-glycosides have been prepared by modifying or eliminating (6, 7, 8) the neighboring-group effect of the 2-substituent. Therefore, in attempting now to synthesize D-mannopyranosyl oligosaccharides possessing the β-(1,2-*cis*-)-linkage, this type of approach has been examined using various derivatives of α-D-mannosyl bromide in the Königs–Knorr reaction.



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Ness, Fletcher, and Hudson found that treatment of 2,3,4,6-tetra-*O*-benzoyl-α-D-mannopyranosyl bromide with methanol in the absence of an acid acceptor produced the α-D-glycoside but not an orthobenzoate (9). Since the latter could have only a transient existence under such acidic conditions it is not surprising that this result contrasts sharply with the extensive production of orthoester from the corresponding acetobromo derivative in the presence of silver carbonate (3, 10). The possibility remained, however, that the participating properties of the benzoxy group under Königs–Knorr conditions might differ sufficiently from those of the acetoxy group to permit formation of relatively more of the inverted (β-D-) product than had been obtained with the acetate (3, 10). Accordingly, the tetra-*O*-benzoyl bromide was treated with methanol containing silver carbonate, but the chief product was an amorphous tri-*O*-benzoyl methyl 1,2-orthobenzoate, and only a small proportion of the β-glycoside was detected. Hence, the characteristics of both acyloxy halides are in reality closely similar. The Königs–Knorr condensation with 1,2,3,4-tetra-*O*-acetyl-β-D-glucose was also examined, and the (1 → 6) linked α-D-disaccharide (1) again was found to be the major biose produced. However, the total yield was considerably better than obtained with the acetobromo derivative (39% vs. 25% (1, 2)), and the proportion of the β-D-linked isomer in the disaccharide fraction was even smaller (5% vs. 14%). It appears advantageous, therefore, to use the *O*-benzoyl bromide rather than the corresponding acetate for the synthesis of D-mannopyranosyl disaccharides possessing the α-configuration.

A high degree of inversion in the reaction of 2-*O*-methyl-α-D-mannopyranosyl fluoride with sodium alkoxide is known to occur (11). The influence of the 2-methoxy group under Königs–Knorr conditions has now been examined using 2,3,4,6-tetra-*O*-methyl-α-D-mannosyl bromide (12). With methanol in the presence of silver oxide this halide produced a mixture of the β- and α-glycosides in the ratio of 3:1, showing again that inversion predominates when the 2-position contains a "non-participating" substituent (see below). Without the acid acceptor, the proportion of β-glycoside was somewhat less, the ratio being 2:1. However, although the effect of the methoxyl group is to favor the formation of β-D-mannosides, its stability limits the usefulness of the *O*-methyl derivative in oligosaccharide synthesis.

For the latter purpose, the *O*-benzyl ether group appeared to offer greater promise as a substituent which should be stable under the condensation conditions but easily removable from the product. 2-*O*-Benzyl-D-mannose (13) was acetylated and the product treated with hydrogen bromide in chloroform, the specific rotation of the bromide indicating that the α-anomer had been formed predominantly. On reaction with methanol in the presence of silver oxide the bromo derivative yielded a levorotatory syrup which was found to contain mainly the β-D-mannoside and only a small proportion of the α-glycoside. However, when the condensation was carried out using 1,2,3,4-tetra-*O*-acetyl-β-D-glucose as the hydroxylic component, the product, following hydrogenolysis and deacetylation, proved to be predominantly 6-*O*-α-D-mannopyranosyl-D-glucose.

The possibility of using a D-mannosyl halide unsubstituted in the 2-position was also examined briefly, by analogy with the use of glycosyl halides containing a free 2-hydroxyl group in the D-glucose (14), 6-deoxy-D-glucose (15), and pentafuranose (see 16) series. For a preparation of a corresponding D-mannosyl halide, 3,4,6-tri-*O*-acetyl-D-mannose (17, 18) was treated with hydrogen bromide, affording a strongly dextrorotatory (and hence presumably the α-1-bromide) syrup. When the latter was condensed under Königs–Knorr conditions with methanol, a mixture of α- and β-glycosides (ratio of approximately 3:1) was formed, and of the disaccharides produced with 1,2,3,4-tetra-*O*-acetyl-β-D-glucose, the β-isomer comprised only a trace proportion.

The properties of a different type of 2-substituted D-mannosyl bromide, the 2,3-*O*-carbonate, were also examined under Königs–Knorr conditions and with this bicyclic derivative inversion was found to occur both with methanol and 1,2,3,4-tetra-*O*-acetyl-β-D-glucose as hydroxylic components. In two previous instances a 2,3-*O*-carbonate derivative has been used successfully to prepare a 1,2-*cis*-glycoside from a 1,2-*trans*-halide, i.e. in the D-mannofuranose (19) and D-ribofuranose series (20). In the current study the halide used was 4,6-di-*O*-acetyl-2,3-*O*-carbonyl-α-D-mannopyranosyl bromide (VI), preparation of which involved the following steps:

benzyl α-D-mannopyranoside (BM) → 6-*O*-trityl-BM
→ 2,3-*O*-carbonyl-6-*O*-trityl-BM → 2,3-*O*-carbonyl-BM
→ 4,6-di-*O*-acetyl-2,3-*O*-carbonyl-BM → 4,6-di-*O*-acetyl-2,3-*O*-carbonyl-D-mannose → 1,4,6-tri-*O*-acetyl-2,3-*O*-carbonyl-D-mannose → VI.

With methanol in the presence of silver oxide, VI afforded a syrupy product which, on treatment with barium methoxide followed by acetylation, gave methyl 2,3,4,6-tetra-*O*-acetyl-β-D-mannopyranoside; only a trace of the α-anomer was detected. The product obtained by condensing VI with 1,2,3,4-tetra-*O*-acetyl-β-D-glucose was also treated with barium methoxide, and the free disaccharide fraction was isolated by cellulose column chromatography. This was found to consist almost entirely of the β-isomer, which crystallized readily from the mixture. A sample of syrupy 6-*O*-β-D-mannopyranosyl-D-mannose was also prepared by condensation of VI with 1,2,3,4-tetra-*O*-acetyl-αβ-D-mannose.

By oxidation of the synthesized 6-*O*-β-D-mannopyranosyl-D-glucose with 2 moles of lead tetraacetate (to obtain the 4-substituted D-erythrose derivative (21)), and then reduction of the product with sodium borohydride, 4-*O*-β-D-mannopyranosyl-D-erythritol (1-*O*-β-D-mannopyranosyl-L-erythritol) (22, 23) was prepared. This result, therefore, confirms by synthesis the earlier assignment based on isotopic data (23) of the configuration of the tetritol unit in this metabolite from *Ustilago* species (PRL 627).

DISCUSSION

The foregoing results, and other data obtained with 2,3,4,6-tetra-*O*-acetyl-α-D-mannosyl bromide (1, 2, 3) show wide variations in the steric properties of different α-D-mannosyl bromide derivatives. However, there are two general patterns evident and these appear to be associated with a change in the reaction medium. The disaccharide syntheses (except those carried out with the 2,3-*O*-carbonate) are characterized by retention of configuration, and necessarily involve the use of an "inert" solvent. For the methyl glycoside syntheses, in which methanol serves both as solvent and hydroxylic component, inversion and orthoester formation are the more prominent features.* These findings are analogous to those of Isbell and Frush (3) on the methanolysis of 2,3,4,6-tetra-*O*-acetyl-α-D-mannosyl bromide in the presence of silver carbonate. They found that the β- (but not α-) D-glycoside is formed, in addition to orthoacetate, when methanol alone is the medium, but that in the presence of ether or benzene as diluent more of the α- than β-D-mannoside, and much less orthoacetate, is formed. A similar mixture of the corresponding dimeric products is obtained using chloroform as solvent when the hydroxylic component is 1,2,3,4-tetra-*O*-acetyl-β-D-glucose (2).

**In one experiment, tetra-O-acetyl-α-D-mannopyranosyl bromide was condensed with 1,2,3,4-tetra-O-acetyl-β-D-glucose using a fourfold excess of the latter and chloroform sufficient only to produce fluidity. Such conditions approximated those used for methyl glycoside synthesis and, in fact, altered the ratio of α- to β-disaccharide produced from about 6:1 to about 2:1.*

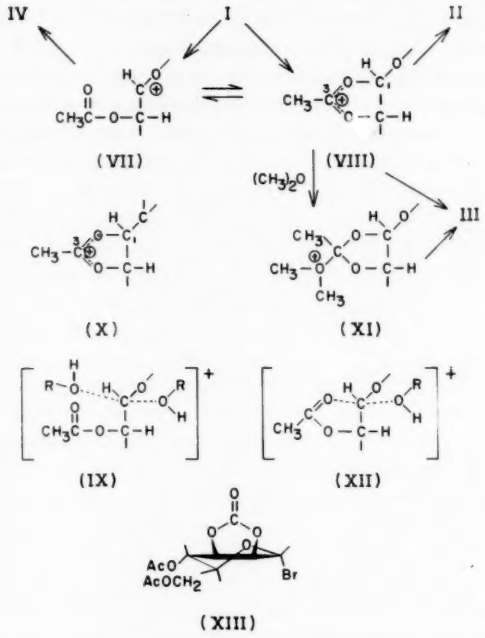
Formation of the α-D-mannoside was accounted for by Isbell and Frush in terms of neighboring-group participation by the 2-acetoxy group. In more recent years additional evidence for a neighboring-group effect of this kind in many other nucleophilic substitution reactions that lead to retention of configuration has been accumulated (see especially ref. 24). Hence it may be inferred that the examples of retention observed in the synthesis of α-D-mannopyranosyl disaccharides also involve neighboring-group participation. With the D-mannose derivatives used several such possibilities can be recognized. The 2-*O*-benzoyl, as well as the 2-*O*-acetyl, derivative reacts with methanol to give the 1,2-orthoester in high yield, a direct demonstration of a neighboring-group effect, and also *dimeric* 1,2-orthoesters are known in the acetate series (2, 25). Participation by the 6-acetoxy group appears to be feasible in reactions of the 2-*O*-benzyl and 2-hydroxy derivatives, although in the D-glucose series this group is usually thought to have a minor influence on the steric outcome of substitution reactions at C-1 (14, 26). Also favoring the possibility of retention by the benzyl derivative is evidence that a 1,2-*trans*-alkoxyhalide can form a cyclic alkoxonium ion during silver-ion-assisted replacements (27). With the 2-hydroxy derivative, the 1,2-*trans*-diaxial arrangement is especially favorable for formation of an intermediate 1,2-anhydride (28) which, on further reaction, should afford 1,2-*trans*-products. Apparently this possibility does not arise with the *trans*-diequatorial 1-chloro-2-hydroxy derivatives of 6-deoxy-β-D-glucose (15) and -β-D-glucose (14), which undergo predominant inversion on ethanolysis or acetolysis. However, the structure of the monohydroxy-D-mannosyl bromide is not yet known with certainty, and conclusions about its behavior must therefore be made with reserve.

Although there may be several possibilities for neighboring-group participation in the reactions studied, these possibilities do not account for the marked steric changes that accompany the change in solvent, e.g., little retention or a great predominance of orthoester formation when the diluent is absent. According to current views, substitution reactions of glycosyl halides proceed likely via a unimolecular course (29, 30, 31). This may apply for a solvent of high polarity, such as methanol, but there is the possibility that the characteristics of the reactions themselves may be altered from unimolecular to bimolecular by the transfer to the much less polar media (ether, benzene, or chloroform). However, since the present data do not give information about kinetic order it cannot be assumed that such an alteration occurs. In fact, the direction of the steric changes induced is contrary to what might then be expected: the inverted configuration of the products formed in methanol is even more characteristic of a bimolecular than unimolecular course, whereas the retention found with the media of low ionizing power is rarely a property of S_N2 reactions.

Within the framework of the S_N1 mechanism, Königs–Knorr syntheses involving α-D-mannosyl halides may be considered in terms of ions such as VII and VIII (5, 6, 7, 30). The formation of β-D-mannosides appears to result from attack by the hydroxylic component on VII, at the side opposite to that shielded by the departing halide ion (7). Such a pathway is presumably important when methanol is the solvent. In the media of lower ionizing power the structure of VII may become modified through increased ion pair aggregation, perhaps in such a way as to induce the steric changes observed. Another possibility is that solvation of ion VII in these media involves the formation of intermediates analogous to those described by Doering and Zeiss (32, 24). For example, IX corresponds to the symmetrically solvated ion postulated by them to account for racemization in S_N1 reactions. However, the presence of the various ring substituents on the D-mannosyl analogue in fact renders such an ion unsymmetrical and interactions, notably between the 2,3- and 6-substituents, might favor eventual formation of the 1,2-*trans*-

rather than the less stable 1,2-*cis*- product. Such an outcome should be favored even more when the hydroxylic component is a bulky tetraacetyl hexose molecule than with methanol.

If neighboring-group participation is possible, ion VIII is expected to be more prominent than VII, although an appreciable proportion of the latter may be present (3, 6, 31). It is generally held that orthoester is formed through attack by the hydroxylic component at



C_3 of VIII and that acceptance of the incoming group at C_1 results in retention of configuration (i.e., in formation of the α-D-mannoside). The generation of an intermediate orthoester ion (X) of type VIII during substitution reactions was postulated originally by Winstein and Buckles (33). With cyclohexane derivatives, for example, they found that several solvolysis reactions proceed with complete retention of configuration, which indicated that "open" carbonium ions (analogous to VII) are not involved and that the incoming groups enter at C_1 of the cyclic ion. However, no retention was observed in solvolyses involving hydroxylic components (water or ethanol), which therefore appeared to attack only at C_3 of X, yielding orthoacid or orthoester.

In the Königs–Knorr syntheses it must be assumed that the effect of solvent is such as to favor reaction at C_3 of VIII under some conditions, but also to promote reaction at C_1 under other conditions. According to Isbell and Frush (3), the presence of a high ratio of ether causes a decrease in the yield of orthoacetate and an increase of α-glycoside, from the methanolysis of tetra-*O*-acetyl-α-D-mannosyl bromide, by competitive solvation of a bimolecular transition complex. In accord with more recent views this suggestion has been modified (6, 7) in terms of the ion VIII: in methanol the favored substitution site is at C_3, but competitive solvation by nucleophilic ether (as in XI, e.g. (6)) permits a rearward attack at C_1 to take place. However, the same explanation does not account

adequately for the results of the disaccharide syntheses, in which retention occurs to an even greater degree, because the diluents used have much less nucleophilic character. One factor favoring attack at C_1 when the concentration of the hydroxylic component is low, is the possibility (suggested by S. Winstein, private communication) that solvation of the departing halide ion by the hydroxylic component promotes an "orientation" of the latter in the vicinity of C_1. Further, it may be noted that substitution at C_1 involves a ring-opening step, and Winstein and Buckles regard this step as having S_N2 characteristics (33). Hence it is conceivable that an effect of decreasing solvent polarity is to increase the rate of substitution at C_1 relative to that at C_2 (34).

Another type of transition state which may be visualized is one intermediate between solvated forms of ion VII (IX) and solvated forms of VIII; for example, XII. Such an ion should be more prominent with a non-polar diluent present than in methanol, because under the former conditions the neighboring nucleophilic acyloxy (or alkoxy) substituent should be able to compete more effectively with the hydroxylic component as a solvating species. Presumably, an α-D-mannoside would be the product of this pathway.

Still other factors may affect the steric outcome of these syntheses. For example, Talley, Reynolds, and Evans (2) showed that in the reaction of tetra-*O*-acetyl-α-D-mannosyl bromide with 1,2,3,4-tetra-*O*-acetyl-β-D-glucose, the presence of iodine suppresses the yield of dimeric orthoester and increases the yield of (α-linked) disaccharide. Iodine is likewise used in the current disaccharide syntheses. In turn, the iodine appears to depress the catalytic effect of the silver oxide on the rate of dissociation of the glycosyl halide (25).

The 2,3-*O*-carbonyl-α-D-mannosyl bromide is exceptional in that it undergoes inversion under both sets of reaction conditions. Molecular models suggest that the carbonate group present cannot participate readily in substitution reactions at C-1, and hence that retention of configuration should be obviated on this basis. However, it appears much more probable that this halide, in contrast to the monocyclic halides used, can react via a bimolecular course, thus ensuring inversion. This possibility arises from the fact that the fused 5-membered carbonate ring modifies the conformation of the pyranose ring (e.g., as in XIII) (35, 36) in such a way as to resist formation of a planar carbonium ion about C-1.

EXPERIMENTAL

Paper chromatography was carried out with Whatman No. 1 paper using (A) butanol:ethanol:water (40:11:19) and (B) ethyl acetate:pyridine:water (10:4:3) as solvents, and (C) *p*-anisidine hydrochloride or (D) ammoniacal silver nitrate as spray reagents. Evaporations were carried out under reduced pressure at 40–45° C and optical rotations measured at 26°±2° C. Silicic acid used in chromatography had a mesh size of 100 to the inch.

*3,4,6-Tri-O-benzoyl-*D*-mannopyranose-1,2-methyl Orthobenzoate*

Amorphous 2,3,4,6-tetra-*O*-benzoyl-α-D-mannopyranosyl bromide (9) (0.45 g) was added to a suspension of silver carbonate (1.5 g) in absolute methanol (15 ml). The mixture was shaken for 2 hours, filtered, the filtrate and washings were concentrated, and the syrup obtained was extracted into ether. Evaporation of the ether afforded a white, amorphous solid (0.35 g); $[\alpha]_D$ −124° (*c*, 1.4, methanol). Calculated for $C_{35}H_{30}O_{10}$: C, 68.8%; H, 5.1%; total benzoate, 4.0 moles; *O*-benzoate, 3.0 moles. Found: C, 68.5%; H, 4.95%; total benzoate (acid *plus* alkali hydrolyzable), 3.91 moles; *O*-benzoate (cold alkali saponifiable), 3.05 moles.

Examined by deacylation with sodium methoxide followed by paper chromatography, the product was shown to contain a trace of methyl β-D-mannoside. When treated with 0.3% methanolic hydrogen chloride the orthobenzoate (14 mg/ml) showed an optical rotatory change from α_D −1.53° (1 dcm, initial) → −0.37° (3 minutes, constant) (cf. ref. 37).

D-Mannopyranose-1,2-methyl Orthobenzoate

The tribenzoyl orthobenzoate (0.1 g) in methanol (5 ml) was treated with a slight excess of barium methoxide for 1 hour, the solution was neutralized with barium carbonate, and evaporated. Water was added to the resulting syrup, the suspension was filtered, and the filtrate extracted three times with chloroform to remove methyl benzoate. On concentrating the aqueous layer an amorphous product ($R_{mannose}$ 3.7, solvent A) was obtained; this product contained a phenyl group (ultraviolet spectrum) but no ester group (infrared spectrum). In 0.02 *N* sulphuric acid (1.2 ml) the observed rotation of the material (22.6 mg) changed from α_D −0.51° (initial, 1 dcm) → +0.18° (20 minutes, constant), and the presence of 0.9 benzoate groups saponifiable with cold alkali was then found (calculated, 1.0 benzoate groups).

6-O-α-D-Mannopyranosyl-D-glucose

To a mixture containing 1,2,3,4-tetra-*O*-acetyl-α-D-glucose (0.52 g), silver oxide (1.0 g), iodine (0.5 g), and Drierite* (5.0 g), in dry dichloromethane (10 ml), was added, with shaking, a solution of 2,3,4,6-tetra-*O*-benzoyl-α-D-mannosyl bromide (1.0 g) in dichloromethane (5 ml); the addition was made in five equal portions over a period of 4 hours. More silver oxide (0.3 g) was added and the mixture shaken for a further 18 hours, filtered, and the filtrate was concentrated to a syrup. Yield, 1.2 g.

A benzene solution of the product was extracted three times with water (which removed most of the monomeric material present), the benzene was evaporated, and the residue was treated for 2 hours with excess sodium methoxide solution. After acidification with acetic acid the reaction mixture was concentrated, taken up in water, and oily material present (methyl benzoate) was extracted into chloroform. The aqueous phase was then transferred to a column of coconut charcoal (38), which was eluted with 5%, and then 15% ethanol. The latter eluate contained most of the disaccharide fraction which, after purification with mixed ion-exchange resins, was recovered as an amorphous solid. Yield, 0.20 g. $[\alpha]_D$ +70° (*c*, 1.8, water); after addition of excess sodium metaperiodate to the solution the equilibrium rotation was $[\alpha]_D$ +73° (assuming conversion of 18 mg of the disaccharide to 10 mg of trialdehyde (39)). (Based on the data given in ref. 39, the latter rotational value corresponds to that of an α,β-mixture of about 95:5.) The product was chromatographically indistinguishable from 6-*O*-α-D-mannopyranosyl-D-glucose (solvent B); none of the β-isomer (see below) was detected. In agreement with the presence of a (1 → 6) linkage the compound rapidly consumed 2.0 moles of lead tetraacetate per mole (21). Calculated for $C_{12}H_{22}O_{11}$: C, 42.1%; H, 6.5%. Found: C, 41.9%; H, 6.6%.†

Reaction of 2,3,4,6-Tetra-O-methyl-α-D-mannosyl Bromide with Methanol

A solution of 1-*O*-acetyl-2,3,4,6-tetra-*O*-methyl-α-D-mannose (12) (0.25 g) in chloroform (0.7 ml) was treated with 30% hydrogen bromide in acetic acid (0.5 ml) for 3 hours. More chloroform was added, the solution was extracted successively with ice water, cold sodium bicarbonate solution, and ice water, and dried. A yellow syrup (215 mg) was obtained on

**Anhydrous calcium sulphate.*

†The β-octaacetate of this disaccharide is amorphous (2). Attempts to convert the compound to a 2,5-dichlorophenylhydrazone or, by reduction, to the corresponding biitol yielded amorphous products.

evaporation of the solvent; $[\alpha]_D$ +210° (*c*, 2, benzene).* This product appeared to be highly unstable and in the following experiments was used immediately after preparation:

(*a*) The bromide (50 mg) in benzene (0.5 ml) was added with vigorous shaking to methanol (5 ml) containing silver oxide (50 mg). After 4 hours the suspension was filtered and the filtrate evaporated to give a syrup (45 mg); $[\alpha]_D$ −39° (*c*, 2, methanol). Examination of this syrup by gas–liquid chromatography, under conditions described by McInnes *et al.* (40), indicated that it consisted of a mixture of methyl α- and β-D-mannosides in a ratio of approximately 1:3.

(*b*) The bromide was treated with methanol as in (*a*) but no silver oxide was added; in 15 minutes the solution showed $[\alpha]_D$ −20° (constant). Excess silver carbonate was added and the solvent was evaporated. Examined by gas–liquid chromatography, the syrup isolated was found to contain an α,β-glycoside mixture in the ratio of about 1:2.

Königs–Knorr Syntheses Using 3,4,6-Tri-O-acetyl-2-O-benzyl-α-D-mannopyranosyl Bromide

2-*O*-Benzyl-D-mannose† (13) (93 mg) was heated at 100° C for 2 hours in acetic anhydride (5 ml) containing sodium acetate (100 mg). Excess anhydride was destroyed with ice water and the solution extracted with chloroform. Evaporation of the extract yielded 1,3,4,6-tetra-*O*-acetyl-2-*O*-benzyl-αβ-D-mannopyranoside (153 mg); $[\alpha]_D$ +7° (*c*, 0.8, $CHCl_3$).

The acetate was dissolved in chloroform (20 ml) containing an excess of hydrogen bromide.‡ The specific rotation soon became constant: $[\alpha]_D$ +40° (2 minutes) → +66° (10 minutes, constant value). After 15 minutes the solution was evaporated and residual hydrogen bromide removed by repeated evaporation of added benzene (3 times).

(*a*) Half of the above bromide was shaken overnight with methanol (3 ml) containing silver oxide (200 mg). The product obtained after filtration and evaporation of the solution had $[\alpha]_D$ −24° (*c*, 1.9, $CHCl_3$) and, after deacetylation, was found chromatographically to contain two components (solvent A, spray C). The main component had R_F 0.69 and the minor R_F 0.77 and by analogy with the R_F's of the corresponding methyl mannopyranosides in the same solvent the slower material should have the β-configuration. This observation agrees with the specific rotation of the product being much closer to that of methyl-β-tetra-*O*-acetyl-β-D-mannopyranoside (−50°) than of the α-anomer (+49°).

(*b*) To the other half of the bromide was added a mixture of tetraacetylglucose (0.4 g) in chloroform (3 cc) containing silver oxide (200 mg), iodine (67 mg), and Drierite (1 g). After it was shaken for 18 hours, the reaction mixture was filtered and the filtrate evaporated. The syrupy product was dissolved in ethanol and debenzylation was effected by shaking with palladium–charcoal in hydrogen at 40 p.s.i. After repetition of the hydrogenolysis the solution was filtered and evaporated. Deacetylation with sodium methoxide in methanol yielded a mixture of which the disaccharide fraction corresponded preponderantly to 6-*O*-α-D-mannopyranosyl-D-glucose, with only a trace proportion of the β-anomer being detected (solvent B, spray C).

Königs–Knorr Syntheses Using 3,4,6-Tri-O-acetyl-α-D-mannosyl Bromide

Crystalline 3,4,6-tri-*O*-acetyl-α-D-mannose (18) (0.11 g) was dissolved in dichloromethane (5 ml) and the solution was saturated with dry hydrogen bromide. A turbidity soon developed and then cleared within 30 minutes, the observed rotation being α_D

**A syrup having the same specific rotation was isolated also when the 1-O-acetyl-tetra-O-methyl derivative was treated with hydrogen bromide in dichloromethane to constant rotation.*

†Prepared in a manner analogous to that used for preparation of 2-O-methyl-D-mannose (41).

‡Use of hydrogen bromide in acetic acid – chloroform resulted in debenzylation of the acetate.

+2.05° (1 dcm, constant). The solution was concentrated *in vacuo* without application of external heat, benzene was then added, and the concentration repeated; yield, 0.10 g of a yellow syrup, $[\alpha]_D$ +140° (*c*, 3.3, benzene). The syrup was dissolved in benzene (3 ml) and used immediately in the following experiments:

(*a*) A portion of the benzene solution (0.6 ml) was added dropwise with shaking to methanol (0.6 ml) containing silver oxide (40 mg) and iodine (20 mg). After 18 hours the supernatant solution (α_D −0.02°) was treated with excess sodium methoxide and then examined chromatographically. The major products detected on the paper (solvent A, spray D) corresponded to methyl α- and β-D-mannoside (approximate ratio 3:1, visual estimation), and mannose (cf. ref. 24).

(*b*) A portion of the benzene solution (0.6 ml) was added dropwise with shaking over a period of 3 hours to a solution of 1,2,3,4-tetra-*O*-acetyl-α-D-glucose (30 mg) in benzene (1 ml) containing silver oxide (40 mg) and iodine (20 mg). After 18 hours the supernatant solution was treated with excess sodium methoxide and examined chromatographically (solvent B, spray C). The major disaccharide detected corresponded to 6-*O*-α-D-mannopyranosyl-D-glucose, and only a trace of the β-isomer appeared to be present.

The paper chromatographic examinations indicated that minor, unidentified, products were also formed in experiments (*a*) and (*b*).

Reaction of 2,3,4,6-Tetra-O-acetyl-α-D-mannosyl Bromide with Excess 1,2,3,4-Tetra-O-acetyl-β-D-glucose

To a mixture of the bromide (2.0 g), silver oxide (2.5 g) and Drierite (5.0 g) a solution of 1,2,3,4-tetra-*O*-acetyl-β-D-glucose (7.0 g) in dry chloroform (5 ml) was added and the mixture stirred overnight. The solution was diluted with methanol, filtered, and the filtrate was treated with sodium (0.2 g) in methanol. After 3 hours the solution was neutralized with acetic acid and examined on a paper chromatogram (solvent B, spray C). The disaccharide fraction consisted of two materials ($R_{lactose}$ 1.0 and 0.7, solvent B) in a ratio of about 2:1, the former corresponding to 6-*O*-α-D-mannopyranosyl-D-glucose and the latter to the β-anomer. Thus the ratio of the β- to the α-disaccharide was about 3 times as great as when equimolar amounts of the bromide and tetra-*O*-acetyl-β-D-glucose were used in the reaction (1, 2).

Benzyl-α-D-mannopyranoside

Mannose (50 g) was stirred with benzyl alcohol (400 ml) saturated with hydrogen chloride at 60° C until the sugar dissolved. The solution was neutralized with silver carbonate, diluted with methanol, filtered, and evaporated. Benzyl alcohol was removed *in vacuo* at 150° C, the residue (containing benzyl mannosides and a little mannose) was dissolved in a small volume of water and the solution extracted 8 times with ethyl acetate. The extracts were evaporated and the product (37 g) was recrystallized twice from ethyl acetate, with m.p. 131–132° C and $[\alpha]_D$ +74° (*c*, 1.3, H_2O). Calculated for $C_{13}H_{18}O_6$: C, 57.8%; H, 6.7%. Found: C, 57.5%; H, 6.8%.

2,3-O-Carbonyl-6-O-triphenylmethyl-benzyl-α-D-mannopyranoside

A solution of benzyl mannoside (37 g), triphenylchloromethane (50 g) in pyridine (150 ml) was heated at 90° C for 4 hours. The mixture was poured into an excess of aqueous potassium carbonate, which was stirred for 1 hour, and the deposit was collected and chromatographed on a silicic acid column using chloroform as solvent in order to separate the triphenylcarbinol from the 6-trityl-benzyl-α-D-mannoside.

The resulting 6-trityl derivative (35 g) was dissolved in pyridine (210 ml) and cooled

to 0° C. A solution of phosgene (7.5 g) in toluene (55 ml) (42) was added dropwise with stirring over 30 minutes, the mixture then being warmed to 40° C for a further 30 minutes. The solution was evaporated to a syrup, which was fractionated on a silicic acid column. Chloroform eluted a crystalline fraction which was recrystallized from ether and corresponded to 2,3-*O*-carbonyl-6-*O*-triphenylmethyl-benzyl-α-D-mannopyranoside. Yield, 12.4 g. A further crystallization from ether yielded material with m.p. 192–195° C and $[\alpha]_D$ +30° (*c*, 1.0, $CHCl_3$). Calculated for $C_{33}H_{30}O_7$: C, 73.6%; H, 5.6%. Found: C, 73.2%; H, 5.7%.

2,3-O-Carbonyl-benzyl-α-D-mannopyranoside and Its 4,6-Di-O-acetate

The trityl mannoside carbonate (12.0 g), in a mixture of chloroform (30 ml) and acetic acid (10 ml), was detritylated by adding, at 0° C, 12 ml of 32% hydrogen bromide in acetic acid. After 1 minute the mixture was treated with an excess of aqueous sodium bicarbonate, and the aqueous solution then extracted 3 times with ethyl acetate. The product recovered from the extract, which apparently contained unchanged material and decomposition products, was put on to a silicic acid column. Chloroform eluted triphenylcarbinol and unchanged trityl derivative, and acetone then eluted a fraction which crystallized from ether. A further crystallization from ether gave 3.3 g of 2,3-*O*-carbonyl-benzyl-α-D-mannopyranoside with m.p. 122–123° C, $[\alpha]_D$ +77° (*c*, 1.0, $CHCl_3$) and absorption at 1810 cm^{-1} in the infrared region (43). Calculated for $C_{14}H_{16}O_7$: C, 56.7%; H, 5.4%. Found: C, 56.7%; H, 5.5%.

The above carbonate (3.2 g) was dissolved in pyridine (10 ml) containing acetic anhydride (6 ml) and left at room temperature for 6 hours. Excess anhydride was destroyed with ice water and the crystalline deposit which formed was filtered off and recrystallized from ether. Yield, 3.6 g, m.p. 114–115° C, $[\alpha]_D$ +37° (*c*, 1.0, $CHCl_3$). Calculated for $C_{18}H_{20}O_9$: C, 56.8%; H, 5.3%. Found: C, 56.6%; H, 5.5%.

4,6-Di-O-acetyl-2,3-di-O-carbonyl-α-D-mannopyranosyl Bromide

4,6-Di-*O*-acetyl-benzyl-α-D-mannoside-2,3-carbonate (3.6 g) was dissolved in acetic acid (50 ml) containing 10% palladium oxide on charcoal (2.0 g). Debenzylation was effected by shaking overnight at room temperature under a hydrogen pressure of 40 p.s.i. The catalyst was filtered off and the process was repeated twice to complete the reaction, yielding syrupy 4,6-di-*O*-acetyl-2,3-di-*O*-carbonyl-D-mannose (2.8 g); $[\alpha]_D$ −7.5° (*c*, 1.0, $CHCl_3$). This material was acetylated (as for 2,3-di-*O*-carbonyl-benzyl-α-D-mannopyranoside) to give 1,4,6-tri-*O*-acetyl-2,3-di-*O*-carbonyl-αβ-D-mannose (2.5 g) with $[\alpha]_D$ +7.5° (*c*, 1.0, $CHCl_3$).

Bromination at C-1 was effected by treatment of the above material (1.02 g) with 32% hydrogen bromide in acetic acid (20 ml) in dry chloroform (100 ml) for 2 hours at 0° C. The chloroform solution was then washed 5 times with ice water, dried, and evaporated to a syrup (960 mg); $[\alpha]_D$ +55° (*c*, 1.0, $CHCl_3$). In the infrared region the compound absorbed strongly at 1815 cm^{-1} and 1740 cm^{-1}, corresponding to the presence of carbonate and acetate groups, respectively.

Königs–Knorr Syntheses Using 4,6-Di-O-acetyl-2,3-di-O-carbonyl-α-D-mannopyranosyl Bromide

(a) Methanol.—The bromo compound (96 mg) was shaken for 30 minutes with methanol (5 ml) containing silver oxide (300 mg). The product had $[\alpha]_D$ −37° (*c*, 1.0, $CHCl_3$) and absorbed in the infrared region at 1805 cm^{-1} (carbonate carbonyl) and 1740 cm^{-1} (acetate carbonyl), and evidently contained 4,6-di-*O*-acetyl-2,3-*O*-carbonyl-methyl-

β-D-mannopyranoside since, after treatment with excess barium methoxide followed by acetylation, it gave 2,3,4,6-tetra-*O*-acetyl-methyl-β-D-mannopyranoside (crystallized from ethanol), m.p. and mixed m.p. 161–162° C. Only a trace of the α-anomer was present as shown by paper chromatography.

*(b) 1,2,3,4-Tetra-O-acetyl-*D*-glucose.*—A mixture of excess 1,2,3,4-tetra-*O*-acetyl-β-D-glucose (3.0 g) in chloroform (8 ml) containing silver oxide (450 mg), iodine (225 mg), and Drierite (5.0 g) was added to the bromo compound (0.30 g) and shaken for 18 hours. It was then diluted with methanol, filtered, and evaporated to a syrup which was redissolved in methanol and de-esterified with 0.1 equivalents of barium methoxide in methanol for 3 hours. The alkali was neutralized with acetic acid and after dilution with excess water the solution was deionized with Amberlite IR-120 and Dowex-1. Evaporation gave a syrup which was fractionated on a cellulose column. *n*-Butanol saturated with water eluted glucose; butanol–ethanol–water (4:1:1 v/v) gave the disaccharide fraction (132 mg; $[\alpha]_D$ +2° (*c*, 1.0, H_2O)), containing mainly 6-*O*-β-D-mannopyranosyl-D-glucose and a trace proportion of the α-anomer (paper chromatogram, solvent B). The product crystallized readily and two recrystallizations from methanol gave the sugar, with m.p. 209–210° C and $[\alpha]_D$ 0° (2 minutes) → −5° (18 hours, constant value; *c*, 1.0, H_2O). Calculated for $C_{12}H_{22}O_{11}$: C, 42.1%; H, 6.5%. Found: C, 41.8%; H, 6.6%.

*(c) 1,2,3,4-Tetra-O-acetyl-αβ-*D*-mannose.*—Using the same proportions and procedure as with the glucose analogue amorphous 6-*O*-β-D-mannopyranosyl-D-mannose (77 mg) with $[\alpha]_D$ −16° (*c*, 1.0, H_2O) was prepared.

*4-O-β-*D*-Mannopyranosyl-*D*-erythritol from 6-O-β-*D*-Mannopyranosyl-*D*-glucose*

Crude mannopyranosyl glucose (163 mg) was dissolved in water (0.5 ml) plus acetic acid (10 ml) and 2.1 molar equivalents of 1% lead tetraacetate in acetic acid added (21). After 15 minutes, 2.0 molar equivalents of oxalic acid in acetic acid was added, the lead oxalate filtered off, and the solution evaporated to a crust (presumably containing di-*O*-formyl-4-*O*-β-D-mannopyranosyl-D-erythrose). The material was dissolved in water (5 ml) containing sodium borohydride (200 mg) and after an hour excess reagent was destroyed with acetic acid. The solution was treated with Amberlite IR-120, filtered, and the filtrate evaporated to a residue which was dissolved in methanol, and the methanol then distilled off, this procedure being repeated several times. The resulting 4-*O*-β-D-mannopyranosyl-D-erythritol was crystallized 3 times from ethanol to yield 20 mg of material with m.p. 160–162° C, $[\alpha]_D$ −38° (*c*, 1.0, H_2O) and an X-ray diffraction powder diagram indistinguishable from that of an authentic specimen. Calculated for $C_{10}H_{20}O_9$: C, 42.25%; H, 7.1%. Found: C, 42.4%; H, 7.2%.

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PERFLUOROALKYL ARSENICALS

PART III. THE PREPARATION AND PROPERTIES OF SOME NEW TRIFLUOROMETHYL AND HEPTAFLUOROPROPYL ARSINES[1]

W. R. CULLEN

ABSTRACT

The reaction of heptafluoroiodopropane with the appropriate phenyl-iodo-arsine in the presence of mercury yields the compounds $C_3F_7As(C_6H_5)_2$, $(C_3F_7)_2AsC_6H_5$, and $C_3F_7(CH_3)AsC_6H_5$. However, the compounds $(CF_3)_2AsR$ (R = C_2H_5, C_4H_9) are obtained from the reaction of the compounds R_2AsI with mercury and trifluoroiodomethane. The ultraviolet spectra of the heptafluoropropyl-arsines are discussed.

DISCUSSION AND RESULTS

In previous papers (1, 2) the preparation of methyl- and phenyl-trifluoromethyl-arsines was described, the method of preparation being to react the appropriate iodo-arsine with trifluoroiodomethane in the presence of excess mercury: for example

$$(C_6H_5)_2AsI + Hg + CF_3I \rightarrow (C_6H_5)_2AsCF_3 + HgI_2.$$

Alkyl iodides react similarly, though in this case the reaction goes further and arsonium derivatives of triiodomercury(II) are obtained (3): for example

$$(C_6H_5)_2AsI + Hg + 2CH_3I \rightarrow (C_6H_5)_2As(CH_3)_2.HgI_3.$$

In order to investigate the generality of these reactions, the preparation of ethyl- and butyl-trifluoromethyl-arsines and phenyl-heptafluoropropyl-arsines was undertaken.

Diethyltrifluoromethylarsine, b.p. 111°, is obtained by the reaction of diethyliodoarsine with trifluoroiodomethane in the presence of mercury; however, the bulk of the product from this reaction is ethylbistrifluoromethylarsine, b.p. 77°. Ethyldiiodoarsine does not react with trifluoroiodomethane under the same conditions, so this substance as an impurity could not have been the source of the ethylbistrifluoromethylarsine. Similarly, when di-*n*-butyliodoarsine is reacted with trifluoroiodomethane and mercury, the only product isolated is *n*-butylbistrifluoromethylarsine, b.p. 118°, though in this case the same compound is produced by the corresponding reaction using *n*-butyldiiodoarsine. A reasonable explanation of these anomalous results is that an exchange reaction takes place between the initially formed dialkyltrifluoromethylarsine and trifluoroiodomethane, producing the alkylbistrifluoromethylarsine; reactions of this sort are now being studied. The reactions of heptafluoroiodopropane with phenyl-iodo-arsines in the presence of mercury are not complicated by side reactions, and heptafluoropropyldiphenylarsine (b.p. 99–102° (10^{-3} mm)), bisheptafluoropropylphenylarsine (b.p. 128° (68 mm)), and heptafluoropropylmethylphenylarsine (b.p. 123° (69 mm)) can be easily isolated.

All the new arsines are colorless mobile liquids of faint odor; they are stable to oxygen and moisture at ordinary temperatures. Solvolysis studies have been made on these compounds and the results will be reported later. The ultraviolet spectra of the heptafluoropropyl-phenyl-arsines are very similar to those of the trifluoromethyl-phenyl-arsines (4). The wavelengths and extinction coefficients of maximum absorption of these compounds are given in Table I.

[1]*Manuscript received July 10, 1961.*
Contribution from the Chemistry Department, University of British Columbia, Vancouver, B.C.

TABLE I

Wavelengths and molar extinction coefficients of the band maxima

Compound	Methanol λ_{max} (Å)	Methanol $\epsilon_{max} \times 10^{-3}$	Cyclohexane, λ_{max}	Compound	Methanol, λ_{max} (Å)
$(C_6H_5)_2AsC_3F_7$	2708	1.18	2710	$(C_6H_5)_2AsCF_3$	2720
	2637	1.72	2640		2690
	2568	1.98	2570		2575
	2355[i]	8.35	2360[i]		2368
	2225[i]*	12.98	2355[i]*		2240
$C_6H_5As(C_3F_7)_2$	2725	0.84	2725	$C_6H_5As(CF_3)_2$	2718
	2650	1.52	2650		2650
	2590	0.79	2589		2587
	2528	0.55	2528		2530
	2238	9.88	2238		2238
$C_6H_5As(CH_3)(C_3F_7)$	2702	0.44	2705	$C_6H_5As(CH_3)CF_3$	2700
	2634	0.58	2635		2630
	2568	0.52	2571		2565[i]
	2275[i]*	5.69	2275		2210
	2175[i]	7.36	2175		

NOTE: i = estimated from point of inflection.
*Band is actually very weak: the recorded intensity is mainly due to contributions from the very strong short-wavelength absorption and from the other bands recorded above.

All the compounds show a weak series of bands in the region 2520–2730 Å, and by analogy with the interpretation of the spectra of the phenyl-trifluoromethyl-arsines (4) these transitions can be characterized as π–π^* absorptions involving electrons localized in the phenyl groups. The remaining bands in the spectra in the region 2100–2500 Å are much stronger. The bands in the heptafluoropropyl compounds correspond in position number and intensity with those of the trifluoromethyl compounds except for the weak band at ca. 2275 Å in the spectrum of heptafluoropropylmethylphenylarsine. The transitions in this region of the trifluoromethyl compounds have been described as involving electron transfer from the non-bonding electrons on the arsenic to the π orbitals of the phenyl groups (4), and again this description of the transitions can probably be carried over to the corresponding bands of the heptafluoropropyl compounds, even though these bands do not shift toward the blue or only shift a little when the solvent is changed from cyclohexane to the more-polar methanol.

The occurrence of two higher-intensity bands in the spectrum of diphenyltrifluoromethylarsine has been interpreted in terms of the steric effect of the CF_3 group being such as to destroy the equivalence of the two phenyl groups with respect to the arsenic lone pair. The intensity of the transition to the interacting phenyl group (the lower-energy transition since interaction would stabilize the phenyl group with a resulting lowering of orbital energies) was much higher than the intensity of the transition to the non-interacting ring. Models such as were used previously (4) show that the more bulky C_3F_7 group has the same effect in the compound heptafluoropropyldiphenylarsine, so the appearance of two bands in the spectrum of this compound, the one of lower energy being the more intense, is not unexpected. Models also indicate that the phenyl group could interact with the C_3F_7 group in the compound heptafluoropropylmethylphenylarsine and almost certainly interacts in the compound bisheptafluoropropylphenylarsine. However, such interaction alone can not account for the presence of two bands in the spectrum of the former compound. The charge transfer band in triphenylarsine occurs

at ca. 40,300 cm^{-1} (4) so the effect of substituting a C_3F_7 group for a phenyl group is to increase the transition energy by ca. 4500 cm^{-1} (using the energy of low-intensity transition to the non-interacting phenyl group of the compound heptafluoropropyldiphenylarsine). The charge transfer band in methyldiphenylarsine occurs at ca. 41,600 cm^{-1} and the effect of substituting a C_3F_7 group for a phenyl group is to increase the energy of the transition by ca. 4300 cm^{-1} if the 2175 Å band in heptafluoropropylmethylphenylarsine is chosen as the charge transfer band, or by ca. 2400 cm^{-1} if the 2275 Å band is the charge transfer band. Thus it is likely that it is the 2175 Å band which is the charge transfer band. The second transition at ca. 2275 Å is very weak. This could arise from a shift or split of the benzene transition which normally occurs at ca. 2000 Å, but its intensity seems to be too low. A more likely explanation is that it is due to an impurity.

The charge transfer bands in the C_3F_7 compounds occur at higher or equal energies when compared with the corresponding bands in the CF_3 compounds; a result which could indicate that in the first order the C_3F_7 group has a greater electron-withdrawing effect on the arsenic lone pair than does the CF_3 group.

The infrared spectra of these new arsines are recorded in the experimental section. It is hoped to discuss these in detail at a later date when more correlations can be made.

EXPERIMENTAL

Apparatus and Technique

Conventional vacuum techniques were used for the manipulation of volatile reactants and products out of contact with moisture and oxygen. Reactions were carried out in sealed Pyrex tubes in the absence of air and light. Infrared spectra were measured on a Perkin–Elmer Model 21 double-beam instrument with rock-salt optics. Ultraviolet spectra were recorded on the Cary Model 14 spectrophotometer. The solvents were spectroscopic grade methyl alcohol or cyclohexane, and the lower wavelength limit of the instrument was ca. 2100 Å as determined by solvent absorption. Gas-phase molecular weights were determined by Regnault's method. Phenyl-iodo-arsines were prepared by the methods previously described (2).

Reaction of Ethyldiiodoarsine with Trifluoroiodomethane in the Presence of Mercury

Ethyldiiodoarsine was prepared from dichloroethylarsine (5) by reacting the chloroarsine with sodium iodide in acetone (6). The product had a boiling point of 126° (11 mm) (lit. value, 126° (11 mm) (6)). The iodo-arsine (18.2 g), trifluoroiodomethane (57.9 g), and mercury (225 g) were shaken at 20° for 11 days. Trap-to-trap distillation of the volatile contents of the tube showed that only one fraction, trifluoroiodomethane (57.6 g), was present.

Reaction of Diethyliodoarsine with Trifluoroiodomethane in the Presence of Mercury

Diethyliodoarsine was prepared from ethyldiiodoarsine as described by Wigren (7). The diiodoarsine in this case was prepared by the procedure used by Burrows and Turner for the preparation of diiodomethylarsine (8). Crude diethyliodoarsine (35 g), trifluoroiodomethane (76 g), and mercury (250 g) were shaken at 20° for 6 days. The unreacted trifluoroiodomethane was separated from the other volatile contents of the tube by trap-to-trap distillation. The less-volatile fraction (14.5 g) was distilled in a nitrogen atmosphere at 760 mm. The bulk of the material boiled at 77°, but a further small fraction boiling at 111° was obtained. Vapor-phase chromatography was used to obtain samples of these two fractions for analysis. The fraction boiling at 77° was identified as *ethylbistrifluoromethylarsine*. Anal. Hydrolysis with 10% aqueous sodium hydroxide

at 100° for 2 days gave fluoroform corresponding to a CF_3 content of 56.2%. The vapor phase molecular weight was 241. Calc. for $C_4H_5AsF_6$: CF_3, 57%; mol. wt., 242. The fraction boiling at 111° was identified as *diethyltrifluoromethylarsine*. Anal. Calc. for $C_5H_{10}AsF_3$: C, 29.7; H, 5.0; As, 37.1; F, 28.2%; mol. wt., 202. Found: C, 29.9; H, 5.1; As, 37.3; F, 27.9%; mol. wt., 230. The infrared spectra of these compounds showed the following absorption bands: $(C_2H_5)_2AsCF_3$ (liquid film): 2980 (s), 2940 (s), 2885 (m), 2350 (w), 2200 (w), 1466 (s), 1425 (w), 1382 (m), 1243 (m)(sh), 1223 (m), 1138 (vs), 1093 (vs), 1038 (m), 1025 (m), 978 (m), 730 (m), 721 (s); $C_2H_5As(CF_3)_2$ (vapor phase): 2980 (s), 2940 (m), 2888 (m), 2250 (w), 2220 (w), 1854 (w), 1469 (m), 1427 (w), 1394 (w), 1245 (s), 1176 (vs), 1157 (vs), 1124 (vs), 1105 (vs), 1056 (m), 1032 (m), 994 (m), 729 (s).

Reaction of n-Butyldiiodoarsine with Trifluoroiodomethane in the Presence of Mercury

The diiodo-arsine was prepared by reduction of *n*-butylarsonic acid using the procedure described by Burrows and Turner for the preparation of diiodomethylarsine (9). The crude arsine (21 g), trifluoroiodomethane (55.1 g), and mercury (210 g) were shaken at 20° for 26 days. Trap-to-trap distillation of the volatile contents of the tube gave unreacted trifluoroiodomethane (40.3 g) and a colorless less-volatile fraction (10.4 g). The latter fraction was distilled in a nitrogen atmosphere at 760 mm: all distilled in the range 110–118°. A middle cut was taken, and this sample was again distilled. The boiling point was 118°, and the sample was identified as *n-butylbistrifluoromethylarsine*. Anal. Calc. for $C_6H_9AsF_6$: C, 26.7; H, 3.34; As, 27.8; F. 42.2%; mol. wt., 270. Found: C, 27.0; H, 3.48; As, 27.6; F, 42.5%; mol. wt., 290. The infrared spectrum showed the following absorption bands (liquid film): 2958 (s), 2925 (s), 2868 (m), 2210 (w), 1470 (m), 1422 (m), 1386 (m), 1347 (w), 1298 (w), 1265 (m), 1204 (s), 1168 (vs), 1132 (vs), 1115 (vs), 1093 (vs), 996 (vw), 967 (vw), 892 (m), 774 (w), 730 (s), 715 (m)(sh); vapor phase (omitting medium and weak bands): 2970 (s), 2935 (s), 1206 (s)(sh), 1179 (vs), 1156 (vs), 1126 (vs), 1107 (vs), (1081, 1076, 1069) (vs), (750, 744, 731) (s).

Reaction of Di-n-butyliodoarsine with Trifluoroiodomethane in the Presence of Mercury

Crude *n*-butyldiiodoarsine, prepared as described above, was used to prepare di-*n*-butyliodoarsine using the method described by Wigren for the preparation of diethyliodoarsine from ethyldiiodoarsine (7). The crude product was dried over calcium chloride and then distilled at 10^{-3} mm. The main fraction boiled at 78–82°, and analysis showed it to be mainly di-*n*-butyliodoarsine. Anal. Calc. for $C_8H_{18}AsI$: C, 30.4; H, 5.7; I, 40.2%; mol. wt., 316. Found: C, 27.9; H, 5.3; I. 42.3%; mol. wt., 285. The impure iodo-arsine (10.6 g), trifluoroiodomethane (65.2 g), and mercury (210 g) were shaken at 20° for 20 days. The unreacted trifluoroiodomethane was separated from a less-volatile fraction by trap-to-trap distillation. The less-volatile fraction (13 g) was distilled at 92 mm in a nitrogen atmosphere, and all boiled at 59°. Its infrared spectrum was identical with that of *n*-butylbistrifluoromethylarsine. The fraction, when distilled at 760 mm (in nitrogen), boiled at 116–120°.

Reaction of Iododiphenylarsine with Heptafluoroiodopropane in the Presence of Mercury

The arsine (12.6 g), heptafluoroiodopropane (82.5 g), and mercury (210 g) were shaken at 20° for 3 months. Trap-to-trap distillation isolated only heptafluoroiodopropane (71.8 g). The contents of the reaction tube were extracted with benzene, which was then removed by distillation at 760 mm in a nitrogen atmosphere, leaving a slightly colored involatile liquid (10.6 g). This fraction was distilled at 10^{-3} mm, and all the material boiled in the range 99–102°. The liquid was redistilled under the same conditions, and a

colorless middle fraction of b.p. 102° was collected, which was identified as *heptafluoropropyldiphenylarsine* (73% yield). Anal. Calc. for $C_{15}H_{10}AsF_7$: C, 45.2; H, 2.51; As, 18.8; F, 33.4%; mol. wt., 398. Found: C, 45.2; H, 2.48; As, 19.0; F, 33.2%; mol. wt., 387. The infrared spectrum showed the following absorption bands (liquid film): 3060 (m), 1976 (vw), 1955 (vw), 1895 (vw), 1877 (vw), 1806 (vw), 1755 (vw), 1650 (vw), 1580 (w), 1485 (m), 1440 (s), 1383 (vw), 1338 (s), 1265 (s), 1227 (vs), 1208 (vs), 1184 (vs), 1174 (vs), 1110 (vs), 1081 (s), 1074 (s), 1034 (s), 1024 (m), 1000 (m), 988 (vw), 968 (vw), 912 (vw), 895 (m), 824 (s), 750 (s), 738 (vs), 732 (vs), 694 (s), 668 (s).

Reaction of Diiodophenylarsine with Heptafluoroiodopropane in the Presence of Mercury

The arsine (22 g), heptafluoroiodopropane (71.8 g), and mercury were shaken at 20° for 2 months. The contents of the tube were worked up as described in the preceding experiment to give heptafluoroiodopropane (59.8 g) and a slightly colored involatile liquid (5.1 g) which boiled in the range 120–124° (63 mm, nitrogen atmosphere). This fraction was redistilled to give a colorless sample of *bisheptafluoropropylphenylarsine*, b.p. 128° (68 mm) (19% yield). Anal. Calc. for $C_{12}H_5AsF_{14}$: C, 29.4; H, 1.02; As, 15.2; F, 54.2%, mol. wt., 490. Found: C, 29.7; H, 1.09; As, 15.6; F, 53.6%; mol. wt., 460. The infrared spectrum showed the following absorption bands (liquid film): 3060 (w), 1890 (vw), 1830 (vw), 1809 (vw), 1756 (vw), 1655 (vw), 1580 (vw), 1485 (m), 1441 (m), 1336 (s), 1274 (s), 1230 (vs), 1210 (vs), 1185 (vs), 1129 (vs), 1117 (vs), 1078 (s), 9040 (s), 1025 (m), 1000 (m), 970 (vw), 935 (vw), 917 (vw), 893 (m), 820 (s), 750 (s), 740 (vs), 733 (vs), 694 (s), 669 (s).

Reaction of Iodomethylphenylarsine with Heptafluoroiodopropane in the Presence of Mercury

The arsine (12 g), heptafluoroiodopropane (70 g), and mercury (215 g) were shaken at 20° for 1 month. Trap-to-trap distillation gave heptafluoroiodopropane (52 g) and a colorless involatile liquid (6.8 g). The latter fraction, when distilled in a nitrogen atmosphere, boiled at 123° (69 mm); it was identified as *heptafluoropropylmethylphenylarsine* (49% yield). Anal. Calc. for $C_{10}H_8AsF_7$: C, 35.7; H, 2.38; As, 22.3; F, 39.6%; mol. wt., 336. Found: C, 35.6; H, 2.47; As, 22.1; F, 39.5%; mol. wt., 322. The infrared spectrum showed the following absorption bands (liquid film): 3060 (w), 2995 (w), 2900 (w), 2400 (vw), 2300 (vw), 2130 (vw), 1980 (vw), 1952 (vw), 1895 (vw), 1875 (vw), 1802 (vw), 1755 (vw), 1645 (vw), 1580 (w), 1485 (m), 1438 (m), 1418 (m), 1338 (s), 1306 (m), 1268 (s), 1224 (vs), 1206 (vs), 1171 (s), 1110 (s), 1080 (s), 1035 (s), 1000 (m), 900 (m), 854 (s), 822 (s), 749 (s), 740 (s), 733 (s), 694 (s), 668 (s).

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REVERSIBLE N,O-HALOACYL SHIFT IN SERINE DERIVATIVES WITH ANTITUMOR ACTIVITY[1]

I. LEVI, J. W. R. WEED, G. LAFLAMME, AND A. E. KOLLER

ABSTRACT

Large doses of N-dichloroacetyl-DL-serine sodium salt were required to cause regression of Sarcoma-37 in mice. About 56% of the unchanged compound was recovered from the urine. These observations suggest that the antitumor activity may reside in a metabolic product of the N-dichloracetyl serine. It is postulated that the active compound is the corresponding O-dichloroacetyl-DL-serine formed from the N-acyl compound by an in vivo enzymatically controlled shift which takes place via the hydroxyoxazolidine and (or) the oxazoline rings. O-Dichloroacetyl-DL-serine hydrochloride was prepared by treating a suspension of N-dichloroacetyl-DL-serine in anhydrous ether with gaseous hydrogen chloride. The free base, O-dichloroacetyl-DL-serine, is an extremely labile compound and reverts to the N-compound in neutral aqueous solution at room temperature. The hydrochloride salt, however, is stable, in which form it was isolated and characterized. The same compound was prepared from serine and dichloroacetic anhydride in dichloroacetic acid. O-Dichloroacetyl-DL-serine hydrochloride displays an antitumor effect against Sarcoma-37 and Sarcoma-180 in mice. The work has been extended to the monochloro- and trichloro-acetyl derivatives of serine.

INTRODUCTION

It was reported recently (1) that the sodium salt of N-dichloroacetyl-DL-serine (2) depresses the growth of Sarcoma-37 in mice, causing in some animals complete regression of the tumors. Most of the presently known agents which are effective against animal tumors are usually administered in relatively small doses such as milligrams or even fractions of a milligram per kilogram of body weight. The above compound, however, had to be administered in doses of 1 g per kilogram of body weight in order to be effective against the tumor. This considerable non-toxic dose is largely excreted by the kidney as unchanged drug, since approximately 56% of the pure crystalline product was isolated from the urine of cats as well as of humans (3). No metabolic or hydrolytic products were identified.

We would like to suggest, therefore, that the active antitumor agent was not the administered N-dichloroacetyl derivative itself, but rather a metabolic product of this compound. One of the specific characteristics of acyl derivatives of hydroxy amino acids having the hydroxyl and the amino groups in vicinal position is the ability of the acyl residue to migrate reversibly between the nitrogen and the oxygen. It is therefore possible that the compound could readily change into the heretofore unreported O-dichloroacetyl-DL-serine isomer and that, in vivo, both forms of the compound exist in equilibrium

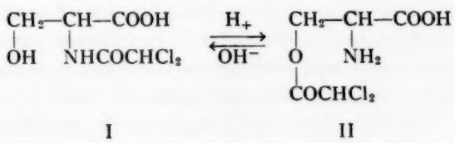

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FIG. 1.

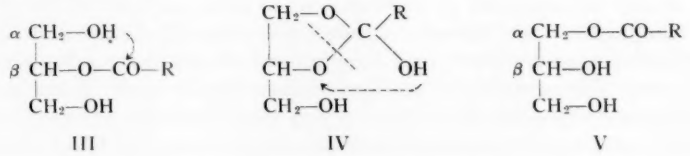
(Fig. 1). Such a concept would explain why large doses of the N-derivative are required to elicit an antitumor effect, since the equilibrium favors the stabilized, less active

[1]*Manuscript received August 15, 1961.*
Contribution from Charles E. Frosst & Co., Montreal, Que.

N-dichloroacetyl-DL-serine. We therefore synthesized O-dichloroacetyl-DL-serine hydrochloride as well as its methyl ester, and preliminary experiments with the former compound do indeed indicate that it is active against Sarcoma-37 in mice at approximately 1/40th the dose of the N-compound and against Sarcoma-180 at approximately 1/20th the dose.

Similar reversible acyl migrations have been studied extensively in vitro over a number of years, in a large variety of compounds, and this shift is now well documented in the chemical literature for the N ⇄ O, N ⇄ S, and O ⇄ O systems. For example, acyl migrations for the N ⇄ O system have been reported for orthoaminophenols (4–12), alkylaminoethanols (13–23), adrenaline (24), noradrenaline (25, 26), ephedrine (26–30), phenylserine (31), aminophenylpropanediols including chloramphenicol (32–35), 2-aminocyclohexanol (36, 37), 2-aminocyclopentanol (38), and aminosugars (39, 40). Similar acyl shifts from oxygen to oxygen have been observed in sugars (41, 42) and glycerides (43–47), and more recently in the N ⇄ S system of cysteine (48) and glutathione (49, 50).

Emil Fischer (51) first proposed a mechanism to explain such migrations from oxygen to oxygen in the case of glycerides of fatty acids. He postulated an unstable five-membered hydroxy-orthoester as an intermediate when an acyl group migrated from one hydroxyl group to another in a 1,2-diol, as shown in Fig. 2. This hypothesis received its first confirmatory support from Hibbert and co-workers (52, 53), who isolated 2-hydroxy-2′-trichloromethyl-1,3-dioxolane, which is analogous to the cyclic intermediate IV postulated by Fischer.



III IV V

FIG. 2. Acyl migration in glycerides.

Today this mechanism involving transient cyclic intermediates is widely accepted because it satisfactorily accounts for a variety of reversible acyl shifts. Various workers have postulated ortho esters in the case of glycerides (47) and sugars (42), oxazoline or hydroxyoxazolidine rings in the N ⇄ O shifts (20, 28, 38, 39), and the corresponding thiazoline and hydroxythiazolidine rings in the case of N ⇄ S shifts (48). In some cases these cyclic intermediates were actually detected or isolated (20, 48).

More recently Doerschuk (44) carried out the rearrangement of 2-monopalmitin glyceride to the 1-monopalmitin product in the presence of glycerol-1-C^{14} and showed conclusively that the rearrangement mechanism is entirely intramolecular, thus eliminating the possibility of hydrolysis and re-esterification. van Lohuizen and Verkade (45) found that α- or β-monoglycerides in ethanolic hydrogen chloride mutually rearranged to an equilibrium mixture, while Raiford and Lankelma (8) showed a similar equilibrium in the case of acylated orthoaminophenols. It is also established for nearly all the above classes of compounds that the equilibrium distribution of the two different forms in which the acylated molecules can exist in solution depends on pH. Migration takes place from N to O when N-acyl compounds are treated with anhydrous hydrogen chloride with formation of the O-acyl-N-hydrochloride derivatives which in alkaline medium revert to the original N-acyl forms (8, 18, 20, 28, 31, 32, 35, 36, 38, 50, 54). In every case so far studied the N-acyl derivatives were much more stable than either the corresponding

O or S derivatives and indeed the latter always easily reverted to the more stable N-derivatives.

Since most chemical reactions which are catalyzed by enzymes are also susceptible to catalysis by simpler organic and inorganic agents, we postulate as a working hypothesis that the reversible acyl shifts in amino acid derivatives such as serine and cysteine, which, in vitro, are dependent on changes in pH, can be similarly mediated in vivo via the hydroxyoxazolidine (or less likely, the oxazoline) ring by acyl migratases resulting in an equilibrium mixture of the two tautomeric forms (Fig. 3).

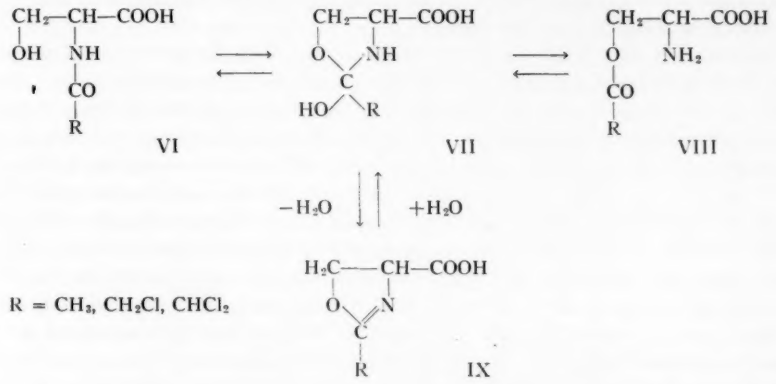


FIG. 3. Reversible N ⇄ O shifts in amino acids.

A corresponding biological shift from O to O, catalyzed by an enzyme, was reported recently by Uziel and Hanahan (55). They described a migratase, which catalyzes the β to α migration of the fatty acyl group on a β-lysolecithin. This enzyme, found in the extracts of *Penicillium notatum* and in commercial pancreatin, is nonhydrolytic in nature. The same migration was effected in the absence of the enzyme by treating the β-lysolecithin with dilute hydrochloric acid. Here again the intermediate formation of an ortho acid was favored to explain this enzymatically controlled intramolecular transesterification. A similar enzyme capable of catalyzing the intramolecular acyl migration in the N ⇄ O or N ⇄ S systems has not yet been described.

The relationship between this type of shift and biological activity has already been observed in the amino acid derivative azaserine (O-diazoacetyl-DL-serine). Here it was shown by Fusari and co-workers (56) that azaserine, in aqueous solution treated with barium hydroxide solution, lost its antibiotic activity as measured against *Kloechera brevis*, and by correlation, its antitumor activity (57), while the diazoacyl group underwent a simultaneous shift from O to N. The resulting barium salt of N-diazoacetyl serine which was isolated possessed little or no microbiological activity in vitro.

DISCUSSION OF RESULTS

It is known that strong acids act as catalysts in the esterification of hydroxy groups with acetic anhydride (58). Acylation of primary amines by acetic anhydride, however, is greatly inhibited when they are present as salts of strong acids (59–61). These facts were utilized in the preparation of O-dichloroacetyl-DL-serine by treating DL-serine with a mixture of dichloroacetic acid and dichloroacetic anhydride. The compound is extremely

labile, tending to change to the more stable N-dichloroacetyl-DL-serine. The hydrogen chloride salt of the O-derivative, however, is sufficiently stable to allow its isolation and storage at room temperature. All attempts to obtain the O-dichloroacetyl base from the crystalline hydrochloride, even under the mildest conditions, failed. For example, neutralization of the hydrogen chloride moiety with an equimolar amount of sodium bicarbonate, at room temperature, resulted in a shift of the dichloroacetyl group from O to N. Similarly, a methanolic solution of O-dichloroacetyl-DL-serine methyl ester hydrochloride (which was prepared by the above procedure from DL-serine methyl ester), upon treatment with one equivalent of triethylamine at room temperature, also underwent this shift to N-dichloroacetyl-DL-serine methyl ester.

The reverse shift of the dichloroacetyl group from N to O was accomplished in the case of N-dichloroacetyl-DL-serine by treating a suspension of the compound in anhydrous ether with a stream of hydrogen chloride gas over a long period of time. Anhydrous conditions are essential, otherwise complete hydrolysis takes place, yielding DL-serine hydrochloride and dichloroacetic acid. When this shift was attempted with the methyl ester of N-dichloroacetyl-DL-serine in anhydrous ether, the unchanged ester was recovered quantitatively, indicating that this compound does not undergo the N → O acyl shift as readily as does the non-esterified compound. Using anhydrous methanol instead of anhydrous ether an intermolecular shift from the N of the amino acid to the O of the alcohol took place rather than the expected intramolecular shift, with the result that serine methyl ester hydrochloride and methyl dichloroacetate were formed. These experiments are summarized in Fig. 4. Although O-dichloroacetyl-DL-serine is a labile compound, it is nevertheless sufficiently stable under the right conditions to be capable of more than transitory existence.

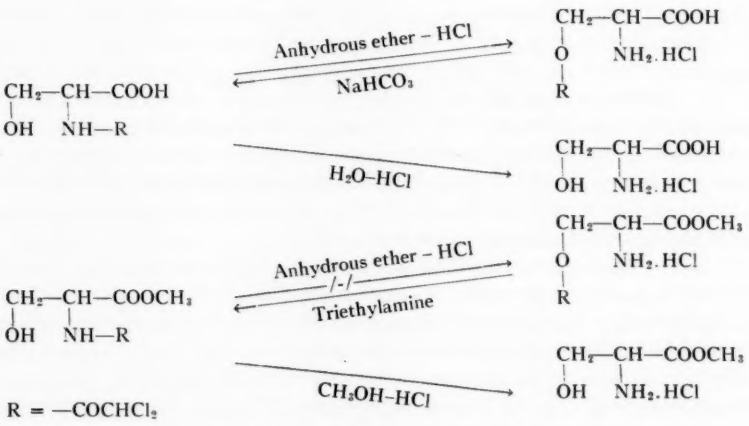


FIG. 4. N ⇄ O dichloroacyl shifts in serine.

Since we were able to show that the postulated reversible N ⇄ O shift of a dihaloacyl group could be effected in vitro, we extended this investigation to the monochloro- and trichloro-acyl compounds of serine. O-Monochloroacetyl-DL-serine was synthesized according to the procedure developed by Sakami and Toennies for the N-acyl derivative (61), and N-monochloroacetyl-DL-serine according to Fischer and Roesner (62). The complete reverse shift of the monochloroacyl group from N to O and O to N was carried

out as for the dichloroacyl compounds. However, in this case O-monochloroacetyl-DL-serine was sufficiently stable to be isolated as the free base as well as the hydrochloride. After this work was completed Benoiton (63) reported the same reversible shift for N-monochloroacetylserine.

All attempts to date to prepare the O-trichloroacetyl derivative have failed. The first synthetic procedure employed was essentially that used for the preparation of O-dichloroacetyl-DL-serine hydrochloride, using benzene as a solvent due to the crystalline state of trichloroacetic anhydride. This yielded instead of the expected O-trichloroacetyl-DL-serine hydrochloride the hitherto unreported O,N-bis(trichloroacetyl)-DL-serine compound. Titration of this compound with alkali indicated an equivalent weight of 199. This agrees with the calculated equivalent weight of 198 based on the finding that the O,N-bis compound is hydrolyzed during the neutralization by the alkali to N-trichloroacetyl-DL-serine (which was isolated and identified) and trichloroacetic acid. The compound gave a negative ninhydrin test in aqueous solution. Its infrared absorption curve indicated the presence of three different carbonyl groups and elemental analyses agreed with the theoretical values for O,N-bis(trichloroacetyl)-DL-serine.

N-Trichloroacetyl-DL-serine was prepared according to the usual Schotten-Baumann procedure (2). An attempt to shift the trichloroacetyl group from N to O under the same anhydrous conditions which converted the N-monochloro- and N-dichloro-acetyl derivatives to the corresponding O-compounds also failed, the unchanged starting material being recovered quantitatively. It is interesting to note that the stability of the amide bond was such in this case that it was not necessary to observe the stringent anhydrous conditions required for the N → O dichloroacetyl shift in order to prevent hydrolysis to serine hydrochloride. Ether saturated with water gave the same result, i.e., there was no hydrolysis of the N-trichloroacetyl group and no N → O shift took place. This unexpected stability to acid of the N-trichloroacetyl group was also observed in the failure of aqueous hydrochloric acid to hydrolyze the latter compound.

This stability was again evident when the O,N-bis(trichloroacetyl) compound was treated with acid in an attempt to prepare O-trichloroacetyl-DL-serine by hydrolysis of the N-acyl group. Contrary to expectations, the O-trichloroacetyl group was the more labile one under these conditions and again N-trichloroacetyl-DL-serine was obtained. This instability of the O-trichloroacetyl group in an acidic medium accounts for the failure, to date, to isolate O-trichloroacetyl-DL-serine.

It therefore appears that in the O-haloacyl series, the stability of the ester linkage decreases as the number of halogen atoms increases. In the N-haloacyl series, however, the opposite situation seems to exist, namely, the stability of the amide bond increases as the number of halogen atoms increases. These effects are no doubt the result of the inductive displacement of the electrons in the direction of the strong electron-attracting chlorine atoms; the greater the number of the latter the more stable the amide bond and the weaker the ester linkage.

These various haloacyl derivatives of serine are presently being evaluated for their antitumor activity in the mouse and rat to determine whether a relationship exists between such activity and the ease of interconversion of the three pairs of isomers.

EXPERIMENTAL

Infrared absorption spectra were determined with a Beckman IR-5 spectrophotometer equipped with a sodium chloride prism, using potassium bromide pellets. Melting points obtained with a Fisher–Johns apparatus, boiling points, and temperature readings are uncorrected and are in degrees Centigrade.

*O-Dichloroacetyl-*DL*-serine Hydrochloride*

DL-Serine (105 g, 1.0 mole) was dissolved in redistilled dichloroacetic acid (500 ml) in a 3-liter, three-necked, round-bottomed flask fitted with a dropping funnel, thermometer, and calcium chloride drying tube. The clear solution was cooled in an ice-water bath and stirred continuously with a magnetic stirrer. A slow stream of dichloroacetic anhydride (312 g, 1.3 mole) was added during 2½ hours at such a rate that the temperature of the reaction mixture did not exceed 32–33°. The flask was allowed to stand overnight at room temperature, and the product was then converted to the hydrochloride salt by passing a slow stream of hydrogen chloride gas into the solution for 1 hour. The excess hydrogen chloride was removed under reduced pressure, anhydrous benzene (1250 ml) was added, and the flask was refrigerated. The product crystallized as a fine white granular material which was removed by filtration, washed with anhydrous benzene, followed by petroleum–ether (30–60°), and dried at 45° in a vacuum oven. Weight 85.0 g, m.p. 115–120°. A second crop of product (5.4 g) was recovered from the filtrate, total yield 35.8%. The product was recrystallized from anhydrous acetone–ether, yielding 29.4% pure crystalline O-dichloroacetyl-DL-serine hydrochloride, m.p. 125–126°, which was soluble in water, ethanol, acetone, tetrahydrofuran, and dioxane, and insoluble in ether, chloroform, and ethylene dichloride. It gave a positive ninhydrin test. Anal. Calc. for $C_5H_8Cl_3NO_4$: C, 23.78; H, 3.19; N, 5.55. Found: C, 23.88; H, 3.29; N, 5.61.

This product was also prepared by saturating a suspension of 3.0 g (0.0286 mole) of DL-serine in 100 ml of dichloroacetic acid with hydrogen chloride gas at 0°. The resulting clear solution was kept at room temperature for 48 hours. The addition of anhydrous ether (100 ml) caused a rapid crystallization of crude product as white crystals. Weight 5.4 g (74.9% yield). The infrared absorption curve of this product was identical with that of the O-dichloroacetyl-DL-serine hydrochloride prepared above.

*O-Dichloroacetyl-*DL*-serine Hydrochloride from N-Dichloroacetyl-*DL*-serine: N → O Dichloroacyl Shift*

Finely pulverized N-dichloroacetyl-DL-serine (2.0 g) (2) was suspended in 100 ml anhydrous ether in a 200-ml round-bottomed flask. A moderately rapid stream of hydrogen chloride was passed into the suspension for 6½ hours. The flow was discontinued overnight and then resumed for 1½ hours. Anhydrous ether was added occasionally to maintain the volume of the reaction mixture. There was no sensible heat effect during this reaction. The ether suspension was evaporated to dryness, anhydrous ethyl acetate (75 ml) added, and the contents warmed for approximately ½ hour. The insoluble residue of O-dichloroacetyl-DL-serine hydrochloride (1.65 g, 70% yield) was removed by filtration, washed with ethyl acetate and ether, and dried, m.p. 125–126°. The infrared absorption spectrum of this material was identical with that of the product synthesized by the route described above and a mixed melting point of the two was not depressed. The ninhydrin test was positive.

*N-Dichloroacetyl-*DL*-serine from O-Dichloroacetyl-*DL*-serine Hydrochloride: O → N Dichloroacyl Shift*

A solution of O-dichloroacetyl-DL-serine hydrochloride (5.04 g, 0.02 mole) in 50 ml distilled water was treated at room temperature with a solution of 3.36 g (0.04 mole) sodium bicarbonate in 50 ml of water. The pH of the solution changed from an initial value of 1.10 to 5.60. The neutralized clear solution was concentrated to dryness from a water bath at 30–35° and under reduced pressure. The residue crystallized from water. An infrared absorption curve of the crystalline product was identical with that of pure

N-dichloroacetyl-DL-serine sodium salt (2). It melted at 172–173° and did not depress the melting point of authentic N-dichloroacetyl-DL-serine sodium salt (2). It no longer gave a positive ninhydrin test, indicating a practically theoretical shift from O to N at pH less than 7.

O-Dichloroacetyl-DL-serine Methyl Ester Hydrochloride

DL-Serine methyl ester hydrochloride (15.5 g, 0.1 mole) (2) was dissolved, with gentle heating, in dichloroacetic acid (100 ml) in a 500-ml, two-necked, round-bottomed flask fitted with a dropping funnel, calcium chloride drying tube, and magnetic stirrer. Dichloroacetic anhydride (30.0 g, 0.125 mole) was added dropwise to the clear, stirred solution. No attempt was made to control the very small heat rise during this addition, which required 45 minutes. The solution was allowed to stir for 24 hours at room temperature (23–25°) to complete the esterification. Diethyl ether (100 ml) was then added, followed by sufficient petroleum ether (30–60°) to produce a faint permanent cloudiness, and the flask was refrigerated for 5 hours. The white crystalline precipitate of O-dichloroacetyl-DL-serine methyl ester hydrochloride was removed by filtration, washed with ether (50 ml) then petroleum ether (50 ml), and dried at 30–40° in a vacuum oven. The product (18.8 g, 70.6% yield) was recrystallized from methanol–ether, m.p. 106° (with prior softening at 101°), white needles. It was soluble in water, ethanol, and dioxane, and insoluble in ether, petroleum ether, chloroform, and ethyl acetate. Anal. Calc. for $C_6H_{10}Cl_3NO_4$: C, 27.00; H, 3.78; N, 5.25. Found: C, 27.30; H, 4.19; N, 5.26.

Attempted Conversion of N-Dichloroacetyl- to O-Dichloroacetyl-DL-serine Methyl Ester: Attempted N → O Dichloroacyl Shift

(i) Hydrogen chloride gas was passed through a suspension of N-dichloroacetyl-DL-serine methyl ester (2) (2.0 g) in 100 ml anhydrous ether for 4 hours whereby complete solution took place. Upon evaporation of the ether a quantitative yield of unreacted starting ester was recovered.

(ii) Dry hydrogen chloride gas was passed through a solution of N-dichloroacetyl-DL-serine methyl ester (5 g) in anhydrous methanol (25 ml), for 1 hour. During this period the flask was cooled in an ice–salt bath. The solution was allowed to stand at room temperature for 24 hours and then concentrated to dryness under reduced pressure and at room temperature. The residual pale yellow syrup which solidified completely on refrigeration for several days was crystallized from methanol–ether, yielding 2.65 g of white crystals, m.p. 132–134°, which were identified by mixed melting points and infrared absorption spectra as DL-serine methyl ester hydrochloride.

Conversion of O-Dichloroacetyl- to N-Dichloroacetyl-DL-serine Methyl Ester: O → N Dichloroacyl Shift

Triethylamine (0.696 ml, 0.005 mole) was added at room temperature to a solution of O-dichloroacetyl-DL-serine methyl ester hydrochloride (1.33 g, 0.005 mole) in anhydrous methanol (15 ml). The solution was shaken mechanically for 10 minutes and then concentrated to dryness under reduced pressure and on a water bath maintained at 25°. The residue, which was a mixture of crystalline triethylamine hydrochloride and oil, was extracted with anhydrous ether (75 ml) whereby the latter dissolved leaving 0.7 g of triethylamine hydrochloride. The ethereal solution on evaporation to dryness under reduced pressure at 25° yielded a pale yellow residual oil which slowly solidified on refrigeration. This was crystallized from ether – petroleum ether (30–60°), yielding 0.95 g (82.6%) of white, fluffy crystals of N-dichloroacetyl-DL-serine methyl ester, m.p.

82–83°, which, by mixed melting point and infrared absorption spectra, was shown to be identical with N-dichloroacetyl-DL-serine methyl ester (2).

O-Monochloroacetyl-DL-serine

Monochloroacetic anhydride (121.0 g, 0.708 mole) was dissolved in ethyl monochloroacetate (100 ml) in a 500-ml round-bottomed flask with gentle warming. To the cooled solution there was added, dropwise, a solution of 10.6 g (0.10 mole) DL-serine in 20 g (0.12 mole) of 60% $HClO_4$. The first few increments of this solution did not cause any significant evolution of heat, but, after a period of induction, external cooling was required. On completion of the addition, the solution was heated for 3 hours on a water bath at 55°, then allowed to stand overnight. Slight application of heat was required to redissolve all solids the next day. The dark brown homogeneous solution was diluted with 4 ml of distilled water, which reacted with residual anhydride. Triethylamine (45 g, 0.45 mole) was then added intermittently, with occasional cooling, to neutralize the perchloric acid moiety of the salt. The reaction mixture was poured into 2 liters of ether, whereupon the product separated as a finely divided crystalline powder. It was recovered by filtration, washed and triturated with ether and ethanol, and dried in a vacuum oven. Wt. 16.3 g (89.8% yield), m.p. 122–123° (decomp.). Literature m.p. 122–123° (decomp.) (64). A mixed m.p. with N-monochloroacetyl-DL-serine was depressed. The product was soluble in water, hot ethanol, hot methanol, hot acetone, and insoluble in most other organic solvents. It reacted positive to ninhydrin and positive for chlorine in the flame test with copper wire.

O-Monochloroacetyl-DL-serine Hydrochloride

Finely powdered O-monochloroacetyl-DL-serine (15.0 g) was suspended in ether (100 ml), and a slow stream of hydrogen chloride gas was passed in for 1 hour. During this process the hydrochloride precipitated as it formed. The particle size of the product was much larger than that of the original O-monochloroacetyl-DL-serine. The excess hydrogen chloride and some of the ether were removed under vacuum. The product (13.2 g, 73.5% yield) was recovered by filtration, washed with ether, and dried in a vacuum oven, m.p. 140–142°. Crystallization from acetone–ether containing a little alcohol yielded 11.0 g of a white crystalline material melting at 141–142°, which was very soluble in the lower alcohols and water, and insoluble in ethyl acetate, chloroform, and ether. Anal. Calc. for $C_5H_9Cl_2NO_4$: C, 27.54; H, 4.16; N, 6.42. Found: C, 27.58; H, 4.16; N, 6.24.

Conversion of N-Monochloroacetyl- to O-Monochloroacetyl-DL-serine: N → O Monochloroacyl Shift

Finely pulverized N-monochloroacetyl-DL-serine (2.0 g) prepared according to the method of Fischer and Roesner (62) was treated in essentially the same manner as described above for the N → O shift in N-dichloroacetyl-DL-serine. The resulting O-monochloroacetyl-DL-serine hydrochloride 1.27 g (53% yield) after crystallization from ether–alcohol melted at 141–142° and did not depress the melting point of O-monochloroacetyl-DL-serine hydrochloride prepared as above. The infrared absorption spectra of the two compounds were identical.

Conversion of O-Monochloroacetyl- to N-Monochloroacetyl-DL-serine: O → N Monochloroacyl Shift

O-Monochloroacetyl-DL-serine (10.0 g, 0.055 mole) was dissolved in 27.5 ml of 2 *N* sodium hydroxide solution (0.055 mole NaOH), allowed to stand at room temperature for 3½ hours, and then neutralized with concentrated hydrochloric acid. The solution was

evaporated to dryness, and the residue extracted with warm ethyl acetate (2×40 ml), which was dried over magnesium sulphate. The ethyl acetate was removed by distillation and the residual oil which solidified at room temperature was crystallized from ethyl acetate – petroleum ether (30–60°), yielding 3.35 g (33.5% yield) of product which melted at 120° and was identical by mixed melting point and infrared absorption with N-monochloroacetyl-DL-serine (62).

*O,N-Bis-(Trichloroacetyl)-*DL*-Serine*

A solution of trichloroacetic anhydride (250.0 g) and trichloroacetic acid (132.0 g) in anhydrous benzene (600 ml) was placed in a water bath at 25–30° and maintained at this temperature throughout the reaction. DL-Serine (69.4 g) was added in small portions to the rapidly stirred solution. When addition was complete, solids began to separate out and in a short while the mixture set to a gel. It was allowed to stand at room temperature overnight, then the product was removed by filtration, washed with benzene, and air-dried. The product (90.9 g), which was insoluble in water and gave a negative ninhydrin test, was crystallized from ether – petroleum ether (30–60°), m.p. 176–180° (a highly purified sample melted at 185–186°). Anal. Calc. for $C_7H_5Cl_6NO_5$: C, 21.21; H, 1.27; N, 3.54. Found: C, 21.42; H, 1.28; N, 3.51.

A sample of this O,N-bis-(trichloroacetyl)-DL-serine (1.0 g) was suspended in distilled water and neutralized at room temperature to the phenol red endpoint with 4.9 ml of 1.027 *N* sodium hydroxide solution. The material dissolved completely as the neutralization proceeded. The aqueous solution was concentrated to dryness on a water bath at 25° under reduced pressure. The residual oil, upon the addition of ether, solidified immediately to a white, friable powder which was removed by filtration, washed with ether, and dried. The product melted at 193–195° and weighed 0.5 g, representing a yield of 72.6% based on hydrolysis to N-trichloroacetyl-DL-serine, sodium salt, with which it was identified by mixed melting point and infrared absorption.

*N-Trichloroacetyl-*DL*-Serine*

DL-Serine (10.5 g, 0.10 mole) was dissolved in 2 *N* sodium hydroxide solution (50 ml, 0.1 mole) in a 500-ml, four-necked, round-bottomed flask fitted with a thermometer, motor driven stirrer, and two dropping funnels. The clear solution of the sodium salt of DL-serine was cooled in an ice–salt mixture to approximately 5°. Trichloroacetyl chloride (24.2 g, 0.133 mole) and 2 *N* sodium hydroxide solution (100 ml, 0.2 mole) were then added dropwise and simultaneously from the two dropping funnels to the stirred, cooled solution at such a rate that the reaction mixture remained on the basic side and below 10° throughout the additions. These additions required about 1 hour. The clear, colorless reaction solution was then stirred for 1 hour during which time it was allowed to warm up to room temperature. The solution was then acidified with concentrated hydrochloric acid (10 ml) and evaporated to dryness using a water bath at 55° and reduced pressure. The residual mixture of sodium chloride and clear yellow oil was extracted with hot ethyl acetate (3×100 ml). The combined ethyl acetate extracts, dried over anhydrous magnesium sulphate, were filtered and again evaporated, and the resulting oil was well shaken with petroleum ether (30–60°) (2×50 ml) to remove residual trichloroacetic acid. The product was crystallized from ethyl acetate – petroleum ether, yielding 8.9 g (35.6%) of white crystalline N-trichloroacetyl-DL-serine, m.p. 106–108°. Anal. Calc. for $C_5H_6Cl_3NO_4$: C, 23.97; H, 2.41; N, 5.59. Found: C, 23.62; H, 2.28; N, 5.56.

The sodium salt was prepared by neutralizing a solution of 87 g of N-trichloroacetyl-DL-serine in 100 ml of water with a 2 *N* sodium hydroxide solution, equivalent to 13.9 g NaOH. The clear solution was evaporated under vacuum at 60° to a dry solid, which

was recrystallized from ethanol, yielding 71 g of N-trichloroacetyl-DL-serine, sodium salt, m.p. 192–193°. Anal. Calc. for $C_5H_5Cl_3NO_4Na$: C, 22.04; H, 1.85; N, 5.14. Found: C, 21.96; H, 1.85; N, 5.32.

*Attempted Conversion of N-Trichloroacetyl- to O-Trichloroacetyl-*DL*-serine: Attempted N → O Trichloroacyl Shift*

N-Trichloroacetyl-DL-serine (2.0 g) was suspended in anhydrous ether (125 ml) and treated with a stream of hydrogen chloride gas for 4 hours. After approximately ½ hour, solution was complete and, upon evaporation to dryness, yielded an oil which rapidly crystallized. The product, 2.0 g, m.p. 106–109°, was identical by mixed melting point and infrared absorption with the starting material.

DL-*Serine Hydrochloride*

An analytical sample of DL-serine hydrochloride was prepared by evaporating to dryness an aqueous solution of serine (5 g in 50 ml water) containing 4 ml concentrated hydrochloric acid and crystallizing the residue from hot anhydrous ethanol. The product was recrystallized from ethanol–ether. Weight 5.4 g, m.p. 136°. Anal. Calc. for $C_3H_8ClNO_3$: C, 25.45; H, 5.70; N, 9.90. Found: C, 25.51; H, 5.48; N, 10.05.

Dichloroacetic Anhydride

This compound was prepared according to the procedure employed by Tedder (65). A mixture of phosphoric anhydride (141 g, 1.0 mole) and dichloroacetic acid (129 g, 1.0 mole) in a 500-ml round-bottomed flask was distilled under reduced pressure. The total distillable liquid came over at 116–120° at 16.5 mm, and was collected without regard to boiling point. Infrared absorption analysis indicated that it contained only a trace of unreacted acid. The product was redistilled in the same manner from approximately 3 g of fresh phosphoric anhydride and the distillate was collected at essentially the same boiling point as above. Weight of dichloroacetic anhydride 87.1 g (72.7% yield). In other preparations yields up to 84% were obtained.

Trichloroacetic Anhydride

This product was prepared in the same manner from trichloroacetic acid with phosphoric anhydride and boiled at 145–150° at 110 mm, yield 77.8%.

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STEADY-STATE DEPARTURE IN ENZYME REACTIONS[1]

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ABSTRACT

A method is described for calculating the departure from steady-state conditions in enzyme reactions. This provides an immediate and simple criterion for the validity of the steady-state approximation. Several variations of the general method, differing in the degree of simplicity and in the treatment of initial transients, are formulated and discussed. These methods are applied to the general case of an enzyme reaction following the Michaelis–Menten mechanism. Specific applications are made using the data of Chance and Gutfreund. While in these specific cases the steady-state concentration of intermediate is reasonably accurate, the extent of reaction may easily vary from that calculated by means of the steady state.

INTRODUCTION

Because of the mathematical difficulties involved in the analysis of enzyme kinetics, it is conventional to employ the steady-state approximation (1–3). This approximation is not, however, always valid, and the conventional methods used to determine validity are usually difficult or erroneous. The two principal methods used for criteria involve (1) making an exact numerical analysis of the kinetics in order to determine the faithfulness of the model or (2) using the assumption that the steady-state approximation is valid when the intermediate or complex concentration is small. Alternative (1) suffers by virtue of its difficulty and by virtue of the fact that each numerical analysis is a special case and must be done again for each change in conditions. Alternative (2) has been found erroneous; in certain chain reactions its use leads to an error of four orders of magnitude in predicting the departure from steady-state conditions (4). In view of the serious problems connected with determining the validity of steady-state approximations, a method has been developed by the authors (4–6) which, for each individual case, offers a simple criterion of steady-state validity. The application of this method to enzyme reactions will be developed in the following sections.

METHOD

The departure from steady-state conditions is given in terms of the departure term ϵ, defined by

$$[1] \qquad (\mathrm{I}) = (\mathrm{I})^*(1+\epsilon),$$

where (I) and (I)* are the actual and steady-state concentrations of the intermediate, respectively. Differentiation of this equation leads to

$$[2] \qquad (\mathrm{I})^* \frac{d\epsilon}{dt} + (1+\epsilon) \frac{d(\mathrm{I})^*}{dt} = r_{\mathrm{I}},$$

where r_{I} is the rate of formation of I, $d(\mathrm{I})/dt$, and is a function of the rate constants, the concentrations of stable species, and the departure term ϵ.

The exact solution of equation [2] is equivalent to any other exact treatment of chemical kinetics. Equation [2] is in a form, however, which lends itself readily to approximate methods which are valid when the departure term is small compared with unity. The first step consists of neglecting all terms in ϵ^2, ϵ^3, etc. (such terms appear as a result of

[1]*Manuscript received July 7, 1961.*
Contribution from the Department of Chemistry, University of Utah, Salt Lake City 12, Utah.
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the implicit dependence of $d(I)^*/dt$ and r_I upon ϵ). The next step depends upon a choice between the following methods:

Method 1: With the above approximation, equation [2] is a linear, first-order equation which can be integrated directly by standard methods. It is sometimes necessary to replace reactant concentration terms by their steady-state values. Method 1 gives a good picture of the build-up of intermediate concentration at the beginning of reaction.

Method 1*a*: A somewhat simpler approximation is obtained by dropping each ϵ (not $d\epsilon/dt$) appearing explicitly or implicitly on the left of equation [2]. This procedure has been justified elsewhere (4).

Method 2: An alternate simplification of method 1 is obtained by setting $d\epsilon/dt = 0$. This removes the initial transient or radical build-up from consideration, but generally gives an accurate picture of the subsequent reaction. This approximation makes equation [2] a simple algebraic equation.[1] This equation can, however, be further simplified by means of method 2*a*.

Method 2*a*: In addition to dropping the $d\epsilon/dt$ term, each term on the left-hand side containing ϵ is also neglected. This step is equivalent to the one leading to method 1*a*. It is not quite as accurate if ϵ exceeds 0.1, but it is otherwise very simple. This is illustrated by equation [18].

In general, methods 2 and 2*a* give sufficient information about steady-state departure without the necessity of resorting to methods 1 and 1*a*. For completeness, however, method 1*a* will also be used here in connection with the reaction of enzymes.

APPLICATION TO ENZYME REACTIONS

The mechanism proposed by Michaelis and Menten (7) describes the essential features of many enzyme reactions. The following steps are involved:

$$[3] \qquad E + S \underset{k_2}{\overset{k_1}{\rightleftharpoons}} I \xrightarrow{k_3} E + P,$$

where E represents the enzyme, S the substrate, I the intermediate, i.e., the binary complex between enzyme and substrate, and P the product or products of reaction. The rate equations are

$$[4] \qquad d(I)/dt = k_1(E)(S) - (k_2+k_3)(I),$$

$$[5] \qquad d(S)/dt = -k_1(E)(S) + k_2(I),$$

$$[6] \qquad d(E)/dt = -k_1(E)(S) + (k_2+k_3)(I),$$

$$[7] \qquad d(P)/dt = k_3(I).$$

The steady-state concentration of I is

$$[8] \qquad (I)^* = \frac{k_1}{k_2+k_3}(E)(S).$$

With the substitution of $(E) = (E)_0 - (I)^*$, where $(E)_0$ is the total amount of enzyme, the quantity $(I)^*$ becomes

$$[9] \qquad (I)^* = \frac{(E)_0(S)}{K_m+(S)},$$

where K_m is the Michaelis constant, $(k_2+k_3)/k_1$.

[1] *We have previously stated that method 2 often requires the reactant concentration to be replaced by its steady-state value. This approximation is not necessary when the reactant concentration, rather than time, is chosen as the independent variable. This choice is more convenient, and is used here.*

In order to obtain $d(\mathrm{I})^*/dt$, needed in both methods 1 and 2, equation [9] is differentiated and simplified with the following result:

$$[10] \qquad \frac{d(\mathrm{I})^*}{dt} = \frac{K_m(\mathrm{E})_0}{[K_m+(\mathrm{S})]^2}\frac{d(\mathrm{S})}{dt}.$$

The evaluation of $d(\mathrm{S})/dt$ is made by substituting $(\mathrm{E}) = (\mathrm{E})_0-(\mathrm{I}) = (\mathrm{E})_0-(\mathrm{I})^*(1+\epsilon)$ into equation [5]. The result, after substitution back into equation [10], is

$$[11] \qquad \frac{d(\mathrm{I})^*}{dt} = \frac{K_m(\mathrm{E})_0}{[K_m+(\mathrm{S})]^2}\{-k_1(\mathrm{E})_0(\mathrm{S})+k_1(\mathrm{S})(\mathrm{I})^*+k_2(\mathrm{I})^*+[k_1(\mathrm{S})+k_2](\mathrm{I})^*\epsilon\}.$$

We now proceed to evaluate the expression $r_I = d(\mathrm{I})/dt$ using equations [1], [4], and [9]. This combination gives

$$[12] \qquad r_I = -k_1(\mathrm{E})(\mathrm{S})\epsilon.$$

Substituting $(\mathrm{E}) = (\mathrm{E})_0-(\mathrm{I})^*(1+\epsilon)$, as above, and dropping the term in ϵ^2, we obtain

$$[13] \qquad r_I = -k_1(\mathrm{S})[(\mathrm{E})_0-(\mathrm{I})^*]\epsilon.$$

Equations [9], [11], and [13] provide all the necessary terms in equation [2], and it is now possible to evaluate this equation according to method 1, 1*a*, 2, or 2*a*.

The application of method 1 to the foregoing mechanism proves to be quite complex. While the differential equation is linear, the integral solutions are nonetheless quite involved. Consequently method 1*a*, which gives a result that is nearly as satisfactory, will be employed here. Using this method, equation [2] becomes

$$[14] \qquad \frac{d\epsilon}{dt}+(k_2+k_3)\epsilon = \left[\frac{K_m}{K_m+(\mathrm{S})}\right][k_1(\mathrm{E})_0-k_1(\mathrm{I})^*-k_2(\mathrm{I})^*/(\mathrm{S})],$$

where the term $(k_2+k_3)\epsilon$, equal to $-r_I/(\mathrm{I})^*$, is obtained by combining equations [8] and [12], and the right-hand side of [14] is obtained by combining equations [9] and [11], and dropping the ϵ terms. The term $(\mathrm{I})^*/(\mathrm{S})$ can be replaced by $[(\mathrm{E})_0-(\mathrm{I})^*]/K_m$ in view of equation [8] and the expression $(\mathrm{E}) = (\mathrm{E})_0-(\mathrm{I})^*$. After simplification, equation [14] becomes

$$[15] \qquad \frac{d\epsilon}{dt}+(k_2+k_3)\epsilon = \frac{k_3[(\mathrm{E})_0-(\mathrm{I})^*]}{K_m+(\mathrm{S})}.$$

After the independent variable is changed to (S) rather than t, the solution of [15] can be obtained by the standard methods employed for linear equations:

$$[16] \qquad \epsilon_{1a} = \left\{\exp\left[\frac{K_m^2}{K_{31}}\int\frac{d\ln(\mathrm{S})}{(\mathrm{E})_0-(\mathrm{I})^*}\right]\right\}\left\{\int\frac{-K_m}{K_m+(\mathrm{S})}\exp\left[-\frac{K_m^2}{K_{31}}\frac{d\ln(\mathrm{S})}{(\mathrm{E})_0-(\mathrm{I})^*}\right]\times d\ln(\mathrm{S})+\omega\right\},$$

where $K_{31} = k_3/k_1$ and ω is the integration constant which can be evaluated knowing the initial conditions, i.e., $\epsilon = -1$ and $(\mathrm{S}) = (\mathrm{S})_0$ when $t = 0$. The second integral in the above expression can be evaluated by plotting

$$\left[-\frac{K_m}{K_m+(\mathrm{S})}\right]\exp\left[-\frac{K_m^2}{K_{31}}\int\frac{d\ln(\mathrm{S})}{(\mathrm{E})_0-(\mathrm{I})^*}\right]$$

against ln (S) and integrating graphically. A similar method may be applied for the evaluation of the integral in the exponential parts.

The expression for ϵ_2, obtained from method 2, is

$$[17] \qquad \epsilon_2 = \frac{\left\{1-[(S)+K_{21}]\frac{(I)^*}{(S)(E)_0}\right\}\alpha}{\left[1-\frac{(I)^*}{(E)_0}\right]-\left\{1-2[(S)+K_{21}]\frac{(I)^*}{(S)(E)_0}\right\}\alpha},$$

while method 2*a* yields

$$[18] \qquad \epsilon_{2a} = \frac{\left\{1-[(S)+K_{21}]\frac{(I)^*}{(S)(E)_0}\right\}}{\left[1-\frac{(I)^*}{(E)_0}\right]}\alpha,$$

where $K_{21} = k_2/k_1$ and $\alpha = K_m(E)_0/[K_m+(S)]^2$.

A numerical example of the method described above has been obtained using results on the kinetics of peroxidase by Chance (8). In this work he found the velocity constant, k_1, for the formation of peroxidase-H_2O_2 (intermediate) to be about 1.2×10^7 l. mole^{-1} sec^{-1}; the velocity constant, k_2, for the reversible breakdown of intermediate is $\leqslant 0.2$ sec^{-1}, and the velocity constant, k_3, for the enzymatic breakdown of intermediate is 4.2 sec^{-1}. The initial concentrations are assumed to be $(E)_0 = 10^{-6}$ mole l^{-1} and $(S)_0 = 10^{-5}$ mole l^{-1}. The departure terms obtained by the above methods are plotted in Fig. 1 as a

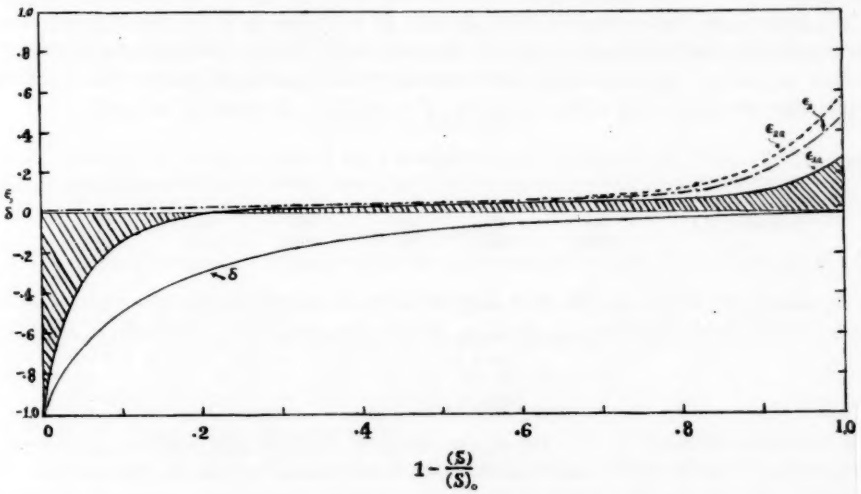

FIG. 1. Departure terms vs. amount of reaction.

function of the fraction of reaction completed. It is seen that ϵ_{2a} is a very good approximation to ϵ_2 over most of the course of the reaction. The values of ϵ_{1a}, which also show the significance of the initial transient, are approximately equal to those of ϵ_2 and ϵ_{2a} after the passage of the initial transient. At 40% reaction, for example, ϵ_2, ϵ_{2a}, and ϵ_{1a} have the values 0.030, 0.032, and 0.028. At 60% reaction the values are 0.034, 0.039, and 0.032, respectively. The departure increases significantly beyond 80% reaction.

The curve calculated by means of method 1*a* shows that the over-all reaction rate, proportional to the intermediate concentration, is, at first, less than that predicted by the steady-state approximation, and then greater (the transition occurs where $\epsilon_{1a} = 0$ at about 20% complete). It is clear that the concentration of product, (P), is not equal to the steady-state value, (P)*. The difference of the two may be expressed in term of δ, defined by (P) = (P)*$(1+\delta)$. This term, representing the fractional departure from the predicted extent of completion of the reaction, is obtained from the equation

$$\delta = \int_0^t (\mathrm{I})^* \epsilon dt \Big/ \int_0^t (\mathrm{I})^* dt, \qquad [19]$$

which is the time average value of the departure of intermediate weighted by the steady-state concentration of intermediate. The integrals in equation [19] are easily evaluated by means of a numerical procedure using previously determined (I)* and ϵ values. The results given in Fig. 1 show that the extent of reaction is significantly less than predicted from steady-state considerations except as the reaction approaches completion.

Another application of the above methods involves two enzyme-catalyzed hydrolysis reactions. Using the Gibson (9) stop-flow method combined with the photoelectric technique, Gutfreund (10) studied the various aspects of these reactions. From this work he estimated $k_1 \geqslant 10^6$ for two systems, trypsin + benzoyl-L-arginine ethyl ester (T + BAEE) and chymotrypsin + acetyl-L-phenylalanine ethyl ester (C + APEE). For both reactions k_3 is of the order of 10. For (T + BAEE), $K_m = 10^{-5}$ and $(k_2 + k_3) \geqslant 10$, whereas $K_m = 7 \times 10^{-4}$ and $(k_2 + k_3) \geqslant 700$ for (C + APEE). For the latter reaction $(k_2 + k_3)$ is so much larger than k_3 that K_m can be regarded as k_2/k_1, the true enzyme–substrate dissociation constant. Applying the same initial concentrations of enzyme and substrate as the previous example, and replacing the equal-to-or-greater-than sign by an equal sign we obtain the values of ϵ_2 for (T + BAEE) as reported in Table I.

TABLE I

Amount of reaction (%)	20	40	60	80	90	95
ϵ_2	.0308	.0390	.0510	.0694	.0826	.0907

It is obvious from equation [17] that $\epsilon_2 \cong 0$ for (C + APEE) since the numerator in equation [17] is negligible when $K_m \cong k_2/k_1$. This is also true for ϵ_{2a} as shown in equation [18].

CONCLUSIONS

The methods proposed in this paper are designed to show the correlation between departure from steady-state conditions and the rate constants used to characterize the mechanism. At this time the major difficulty in applying the above methods stems from the lack of data concerning individual rate constants. Measurement of the rate of product formation or substrate disappearance after the initial transient period does not provide sufficient information for this purpose. Consequently it is usually necessary to resort to some form of transient analysis to obtain the necessary rate constants. One use of the present methods may be found in the simplified transient analysis (method 1*a*) which might be used for the approximate evaluation of rate data. As more such data is accumulated, it should be possible to correlate known rate constants pertaining to a particular step in the general mechanism with the structure of the reactants, and subsequently to

estimate unknown rate constants. This can now be done quite successfully in the pyrolysis of hydrocarbons and related molecules. In this case the methods developed here can be applied directly to determine steady-state validity.

The above methods can also be used to extend the working range of a mechanism study. If an exact transient analysis has been used on experimental data to calculate the rate constants, the present methods are very convenient for the analysis of concentration effects. By contrast, using the exact method, a new and difficult analysis must be made for every variation in concentration. In addition, the effect of temperature changes on the rate constants can be estimated by means of approximate activation energies, and the current methods can be used to roughly estimate the temperature range of steady-state validity. The exact method, again, would involve a lengthy analysis for each temperature.

The limitations of the methods used here are obvious; the calculation of ϵ values which exceed about 0.20 reflect a good deal of error. To obtain more accuracy one would have to apply exact methods. Since the latter alternative is much more complicated, it is well to remember that the simpler methods, such as 2*a*, provide, first, a simple criterion of steady-state validity, and second, an accurate value of ϵ providing only that it is small. Thus, for example, we are able to conclude from Table I that the departure for the (T + BAEE) reaction is not very serious, and also report reliable values for ϵ within the limitations of accuracy of the rate constants. Similarly if we had a system for which ϵ was calculated to be, say, 5.0, we could state conclusively that the steady-state departure is serious, but we could not predict the extent of departure. When considered within this framework, it is felt that the above methods, especially 2*a*, might find a great deal of applicability to the common enzyme reactions for which a doubt exists concerning the validity of the steady-state approximation.

ACKNOWLEDGMENT

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THE BASICITIES OF ORTHO-SUBSTITUTED BENZOIC ACIDS[1]

ROSS STEWART AND MAURICE R. GRANGER

ABSTRACT

The basicities of 15 ortho-substituted benzoic acids have been measured in sulphuric acid. The ortho effects of alkyl groups are base weakening and increase in the expected order methyl, ethyl, *i*-propyl, *t*-butyl. Ortho halo benzoic acids have comparable basicities and are weaker than their para isomers. Oxygen-containing ortho substituents, except hydroxyl, all cause substantial base strengthening relative to the para isomers. Even the groups nitro and carboxyl when substituted ortho in benzoic acid cause the basicity to rise, presumably because of hydrogen bonding in the conjugate acids.

INTRODUCTION

It is well known that the reactivities of ortho-substituted aromatic compounds are not as easily predicted as those of their meta and para isomers. The failure of the Hammett equation in the former cases illustrates this (1, 2). The fact that virtually all ortho-substituted benzoic acids, regardless of the electronic nature of the substituent, are stronger acids than benzoic acid itself has been explained on the grounds of steric inhibition of resonance in the neutral molecule. That is, the bulk of the neighboring group forces the carboxyl group out of the plane of the aromatic ring and thus raises the energy of the neutral molecule relative to the anion in which resonance with the ring will be slight (3, 4). Opposing this acid-strengthening effect will be the steric hindrance to solvation of the anion caused by the nearby ortho substituent (4). In addition to these two general steric effects, there is the electronic effect of the substituent and, in some cases, specific interactions between the substituent and either the carboxyl group or the carboxylate anion.

We have determined the *basicities* of a series of ortho-substituted benzoic acids using the general Hammett technique in sulphuric acid (5–8). In this case, resonance with the ring is more important in the ion than in the neutral molecule and inhibition of resonance by an ortho substituent (9) will here serve to decrease the basicity of the acid. (Since basicities are usually referred to in terms of the strength of the conjugate acid this will raise the acidity of the conjugate acid, i.e. it will make pK_{BH^+} less positive.) Steric hindrance by the ortho group to solvation of the cation will operate in the same direction in this case. Thus one might reasonably expect that in the absence of specific interactions all ortho substituents might be base weakening in the benzoic acid series.

RESULTS AND DISCUSSION

The pK_{BH^+} values for the ortho-substituted benzoic acids are listed in Table I together with spectral data for the neutral and cationic forms. In Table II are listed for comparison the differences in the pK_{HA} and the pK_{BH^+} values for ortho- and para-substituted benzoic acids. ($pK_{HA} = pH + \log HA/A^-$ and $pK_{BH^+} = H_0 + \log BH^+/B$, where $BH^+ \equiv H_2A^+$ and $B \equiv HA$.) One can see that here both base-strengthening and base-weakening effects are present. The electrical effect of an ortho substituent operating through the ring can be very roughly cancelled by assuming that the electrical effects of ortho and para substituents are equal (10, 11) and by using the difference in basicity of the ortho- and para-substituted acids as a measure of the ortho effect. When this is

[1]*Manuscript received July 25, 1961.*
Contribution from the Department of Chemistry, University of British Columbia, Vancouver, British Columbia.

TABLE I

Basicity constants, absorption maxima, and slopes of linear basicity plots for substituted benzoic acids

Substituent	$-pK_{BH^+}$[a]			Slope	In 45% H_2SO_4		In 96% H_2SO_4	
	Gra.	Lin.	Av.		λ_{max}	log ϵ_{max}	λ_{max}	log ϵ_{max}
Hydrogen	7.20	7.15	*7.18*	1.1	233	4.00	261	4.14
o-Methyl	7.15	7.10	*7.13*	1.1	234	3.88	265	4.18
o-Ethyl	7.15	7.15	*7.15*	1.1	233	3.83	266	4.14
o-*i*-Propyl	7.25	7.21	*7.23*	1.2	233	3.71	265	4.06
o-*t*-Butyl	7.57	7.74	*7.66*	1.1	232(sh)	3.36	265	3.73
o-Fluoro	7.54	7.66	*7.60*	1.2	229	3.97	257	4.18
o-Chloro	7.64	7.72	*7.68*	1.2	233	3.79	263	4.11
o-Bromo	7.73	7.76	*7.75*	1.3	236[b]	3.80[b]	265	4.04
o-Iodo	7.74	7.82	*7.78*	1.5	232(sh)	3.84	266	3.87
o-Hydroxyl	6.80	6.75	*6.78*	1.2	237	3.95	260	4.20
o-Methoxyl	6.04	6.16	*6.10*	1.1	240	3.92	262	4.20
o-Ethoxyl	6.05	6.15	*6.10*	1.0	240	3.91	262	4.15
o-Nitro	7.18	6.89	*7.03*	0.8	266	3.69	277	3.74
o-Carboxyl	5.98	5.92	*5.95*	1.0	231	3.83	264[c]	3.89[c]
m-Carboxyl[d]	7.10	7.10	*7.10*	1.0	282	2.97	298	3.23
p-Carboxyl	7.56	7.46	*7.51*	1.0	245	4.28	260	4.43
α-C_4H_4[e]	7.1	—	*7.1*	—	235(s)	4.29	253	4.11

[a] Gra. = graphical method; Lin. = linear method; Av. = average.
[b] In 65% H_2SO_4.
[c] In 87% H_2SO_4.
[d] From $n-\pi^*$ absorption maximum.
[e] α-Naphthyl.

TABLE II

Comparison of the acid and base strengths of ortho- and para-substituted benzoic acids

Substituent	$pK_{BH^+}^{ortho}-pK_{BH^+}^{HBz}$	$pK_{BH^+}^{ortho}-pK_{BH^+}^{para}$	$pK_{HA}^{ortho}-pK_{HA}^{HBz}$	$pK_{HA}^{ortho}-pK_{HA}^{para}$
Hydrogen	0.00	0.00	0.00	0.00
Methyl	0.05	−0.29	−0.29	−0.43
Ethyl	0.03	−0.31	−0.43	−0.58
i-Propyl	−0.05	−0.40[c]		
t-Butyl	−0.48	−0.84	−0.74	−0.94
Fluoro	−0.42	−0.38	−0.93	−0.87
Chloro	−0.50	−0.28	−1.26	−1.05
Bromo	−0.52	−0.33[c]	−1.35	−1.15
Iodo	−0.60	−0.36	−1.34	−1.06
Hydroxyl	0.40	−0.19	−1.22	−1.60
Methoxyl	1.08	0.50	−0.11	−0.38
Ethoxyl	1.08	0.43	0.01	−0.24
Carboxyl	1.23	1.56	−1.25	−0.56
Nitro	0.15	1.00[c]	−2.03	−1.27

[a] Values from present work and from reference 7; the $pK_{BH^+}^{para}$ values used here are 0.08 pK units less negative than those in ref. 7 because of a discrepancy in the benzoic acid determination in the two sets of work.
[b] Values from reference 4, p. 588.
[c] Estimated value.

done one can see that most, but not all, of the ortho substituents are now acid strengthening in the $ArCO_2H_2^+$ series, as they are in the $ArCO_2H$ series. It will be convenient to discuss the results in three groups: (*a*) the alkyl groups, (*b*) the halogens, (*c*) the oxygen-containing groups.

The Alkyl Groups

The trend of the ortho effects of the alkyl substituents on the basicities of benzoic acids is particularly clear. Methyl and ethyl groups exert similar effects, the *i*-propyl group a somewhat larger effect and the *t*-butyl group a considerably larger effect. Similar

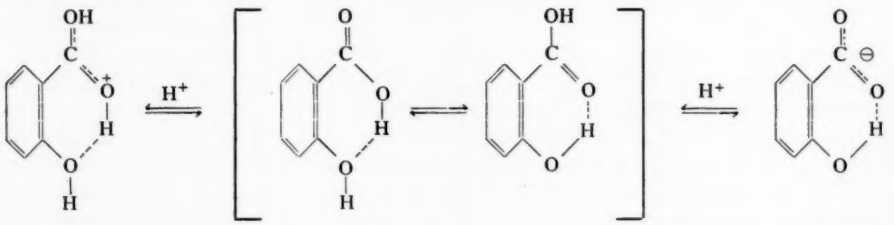
behavior has been observed by Brown and Cahn (12) in the reaction of α-alkyl pyridines with boron compounds. It is interesting that, when ΔpK_{BH^+} (the difference between the basicities of benzoic acid and the ortho isomer) is plotted against the activation energy for the reaction of methyl iodide with the α-alkyl pyridines (12), a linear relation results, indicating that the alkyl substituents are exerting similar effects in both this reaction and the protonation reaction. Since the electrical effects of the alkyl groups are similar, one can conclude that the decrease in basicity as the alkyl groups increase in size is due to steric hindrance to resonance in, and solvation of, the conjugate acid.

The Halogens

Benzoic acids with ortho halogen atoms are all weaker bases than their para isomers and weaker than benzoic acid itself, but their strengths, unlike those of the α-halopyridines, are not greatly different (13). It is probable that hydrogen bonding plus steric effects on resonance and solvation are all operative but it is rather surprising that fluorine, which should have the smallest steric effect on solvation and resonance (base weakening) and which should have the largest hydrogen bonding effect (base strengthening), gives a basicity which is little different from those of the other halogens.

Oxygen-containing Groups

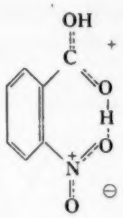
All the oxygen-containing groups exhibit base-strengthening effects relative to benzoic acid itself and all but hydroxyl cause the ortho acids to be stronger bases than their para isomers. The acid-strengthening effect of the *o*-hydroxyl in salicyclic acid is well known and is generally attributed to stabilization of the benzoate anion by internal hydrogen bonding with the hydroxyl group as in II (14, 15).



I II

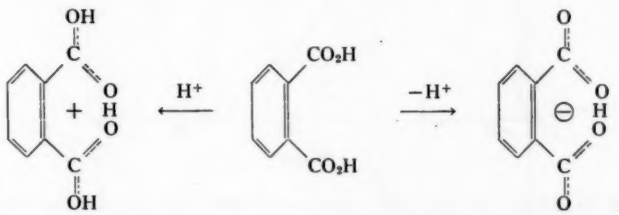
Undoubtedly hydrogen bonding in I stabilizes the cation as hydrogen bonding in II stabilizes the anion, but assessing the relative importance of the above structures is difficult because of the different kinds of protons present. The case of the ortho alkoxy benzoic acids is simpler and it is clear that structures corresponding to I above are responsible for the base-strengthening effect. (The hydroxyl and alkoxyl groups, as expected from earlier work (7), appear to undergo no protonation themselves.)

The nitro and carboxyl groups provide very interesting examples of specific ortho interactions which stabilize the protonated forms. Because of the small spectral shift on protonation, *o*-nitrobenzoic acid gave a poor ionization curve and the pK_{BH^+} listed in Table I must be regarded as approximate only. Nevertheless, it is clear that *o*-nitrobenzoic acid is a much stronger base than its para isomer and is even slightly stronger than benzoic acid itself. This can be attributed to hydrogen bonding in the conjugate acid, viz.



(The reason for the acid strength of *o*-nitrobenzoic acid being so much greater than that of its para isomer is less clear, since no hydrogen bonding is possible in the anion.)

Phthalic acid is much more basic than its meta and para isomers just as it is also more acidic. That is, proton loss from and proton addition to, the ortho dicarboxyl system are both much easier than with the meta and para isomers or with benzoic acid itself. The symmetry of the two ions and their structural similarity can be seen in the following equation.



III

Cation III is a species of some interest since the second ring that is formed by virtue of the hydrogen bridging may have some aromatic character (16). If the hydrogen bonding were strong enough to shorten the oxygen–oxygen bond distance sufficiently to allow some orbital overlap one would have a cyclic system containing six π electrons.

The spectral changes that occur with phthalic acid as the sulphuric acid concentration increases are shown in Fig. 2. Leisten (17) has shown by cryoscopic means that anhydride formation occurs in solutions just above 100% sulphuric acid and the spectrum in 104% acid must be that of the anhydride, probably in its protonated form. The second spectral change which leads to this spectrum is centered at $H_0 = -11.4$. No indication of a second spectral change was observed in the case of isophthalic acid or terephthalic acid even up to 30% fuming sulphuric acid. Probably the protonation of the second carboxyl group in these cases does not give rise to a sufficiently different spectrum to allow detection.

Quantitative Correlations

The parameters, σ^* and E_S, which Taft (1) has used with success to correlate the rates of certain reactions of ortho-substituted compounds, fail in the present case presumably because of resonance effects in the conjugate acid and because of the specific hydrogen-bonding interactions referred to above. There is, however, fair agreement with the Taft equation $\log K/K_0 = \sigma^*\rho^* + E_S$. The modified Farthing and Nam equation (2), $\log K/K_0 = \sigma_{R^+}\rho_{R^+} + \sigma_S\rho_S$, also gives a fair correlation if the widely deviating points for $-NO_2$, $-t$Bu, and $-CO_2H$ are ignored.

It is interesting to note that, when the values for the acidities of ortho-substituted benzoic acids (pK_a) are plotted against the corresponding basicities (pK_{BH^+}) as in Fig. 1,

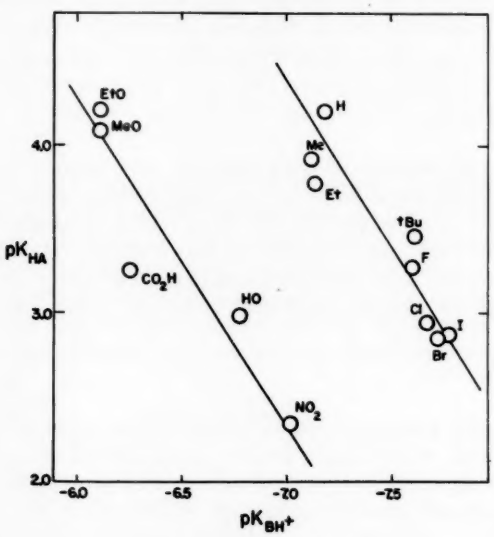


FIG. 1. Plot of the acidities of ortho-substituted benzoic acids (pK_{HA}) against their basicities (as pK_{BH^+}). The point for *o*-CO_2H has been corrected by 0.3 pK units on each axis for the statistical effect of two carboxyl groups on each ionization.

the substituents fall near two straight lines of approximately the same slope, the oxygen-containing substituents near one line and the other substituents near the other. It will be remembered that of the three general effects mentioned in the Introduction—electronic, steric inhibition of resonance, and steric hindrance to solvation—only the latter was expected to operate in opposite directions in the two series and it thus appears to be of the least importance. The specific interactions between the ionized carboxyl groups and the oxygen-containing substituents also show a surprising degree of regularity.

It has been assumed in this discussion that carbonyl protonation occurs exclusively (7). However, if an ortho substituent inhibits resonance with the ring the energy of the carbonyl-protonated form will rise relative to that of the hydroxyl-protonated form, which is not conjugated with the ring in any case, and it is conceivable that hydroxyl protonation may be significant in some cases. Acylium ion formation, which occurs with 2,6-disubstituted benzoic acids in concentrated sulphuric acid, appeared to be absent in the present work.

EXPERIMENTAL

Reagents

The benzoic acids were purified either by several recrystallizations or by vacuum distillation. Samples of *o*-ethyl, *o*-*i*-propyl, and *o*-*t*-butyl benzoic acids were kindly supplied by Professor Harold Schechter. Sulphuric acid solutions were prepared and standardized as before (7).

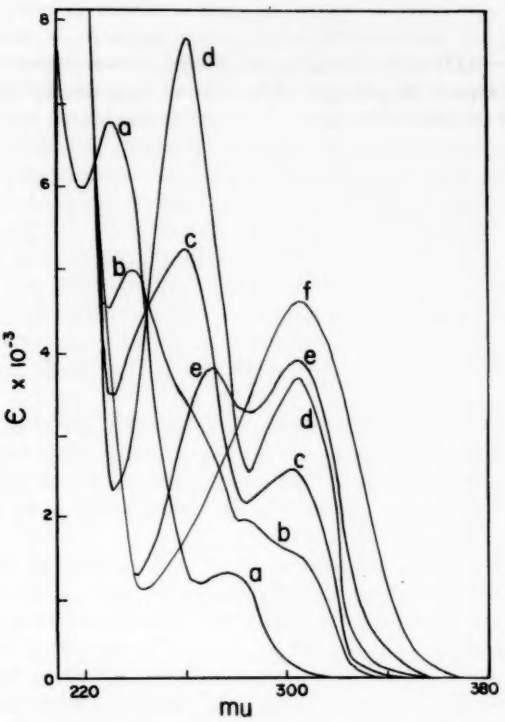


FIG. 2. Ultraviolet absorption spectra of phthalic acid in sulphuric acid solutions: *a* 45%, *b* 70%, *c* 74%, *d* 80%, *e* 100%, *f* 104% H_2SO_4.

Measurement of pK_{BH^+}

This was done by spectrophotometric analysis essentially as previously described (7, 9). In cases of low solubility of the compound in sulphuric acid, stock solutions of the compound were made up in ethanol and 0.05-ml aliquots of this were pipetted into 10-ml volumetric flasks using a 0.100-ml Hamilton syringe with a Chaney adaptor. In these cases the ethanol was not evaporated and a correction was made for the dilution of the sulphuric acid by the ethanol. It was found that the presence of the ethanol in the acid in no way affected the ultraviolet spectrum of the substrate and that identical pK_{BH^+} values, within experimental error, could be obtained by the two methods. Dilution experiments after 1 hour showed that no irreversible changes such as sulphonation were occurring in the concentrated acid.

Calculations

Two methods were used to calculate the pK_{BH^+} values. The first was the graphical method of Davis and Geissman (18) involving the plotting of $D_{\lambda_l} - D_{\lambda_u}$ against H_0 where λ_l and λ_u are wavelengths at which the ion and neutral molecule, respectively, absorb strongly. This produces a "titration curve" from which the inflection point can be read. The following modification of this method was also used (7). Let $\Delta D_B = D_{\lambda_l} - D_{\lambda_u}$ in an acid concentration in which the base is effectively unionized and let $\Delta D_{BH^+} = D_{\lambda_l}$

$-D_{\lambda_u}$ in an acid concentration in which the base is effectively completely ionized and let $\Delta D = D_{\lambda_l} - D_{\lambda_u}$ in the acids which partly ionize the base. It can be shown that a plot of $\log(\Delta D_{BH^+} - \Delta D/\Delta D - \Delta D_B)$ against H_0 should give a straight line of unit slope with the intercept equal to pK_{BH^+}. The advantage of this method is that the need for an arbitrary choice of the inflection point of a curve is eliminated since the best straight line may be found by the method of least squares. However, difficulty is often experienced in choosing appropriate optical densities to correspond to zero and complete ionization since solvent shifts usually occur for both the unionized and ionized forms but particularly for the latter as pointed out earlier by Hammett (5, 6). The result of this is that if the spectrum obtained in, say, 98% sulphuric acid, is used for the completely ionized form of a compound which is half ionized in, say, 60% acid an inflated value for D_{BH^+} results since increasing the sulphuric acid concentration usually produces a red shift and an increased extinction coefficient. This, in turn, results in plots by the "linear method" which are, in fact, frequently linear but which often have non-unit slopes.

We have attempted to cancel the solvent shifts partially by choosing as our values of D_u and D_l those which are obtained by moving 1.5 H_0 units in both directions from the pK_{BH^+} determined by the first method above. The choice of 1.5 units is arbitrary and, if there were no solvent spectral shift at all, would result in an error of about 3% in the assigned values of D_u and D_l.

The slopes shown in Table I are close to unity and, in support of the method used here, the plots were all very good straight lines provided values of the logarithmic function between +1.0 and −1.0 were used whereas if D_u and D_l were assigned, using values many H_0 units away from the pK_{BH^+}, the plots were very often non-linear. It may be mentioned that, when the present method was applied to the data previously obtained with aldehydes, ketones, acids, and amides, somewhat lower slopes were obtained than with the ortho-substituted acids reported here. The values for the former were mostly in the 0.9–1.1 range.

There is always the possibility that the irregularities in the log plots are not caused entirely by solvent effects on the spectra. It is conceivable that weak bases of the carbonyl type studied in this and earlier work are following some acidity function other than H_0, a scale which was established chiefly with the aid of nitrogen bases. The deviations from unit slope listed in Table I are not great, except for *o*-iodobenzoic acid, and we believe that they are caused by solvent effects on the spectra rather than by deviations of the ionization process from ideal behavior (8, 19). If, for example, the ionization process was following the h_R' (20) function rather than h_0 a slope of approximately two would result (18). However, in order to shed further light on the matter we are at present examining systematically the variations in the spectra of carbonium ions, ammonium ions, and oxonium ions with changing sulphuric acid concentration.

The values in Tables I and II are quoted to two decimal places. However, in view of the fact that many of the pK_{BH^+} values were measured in the region 70–80% sulphuric acid where the H_0 scale is considered to be not firmly established and in view of the difficulties caused by solvent effects on spectra, there may well be an absolute error of 0.2 pK units although the relative errors within a series will be less than this.

ACKNOWLEDGMENT

We are grateful to the National Research Council of Canada for financial support, including the award of a Studentship to one of us (M.R.G.).

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TRYPTAMINES, CARBOLINES, AND RELATED COMPOUNDS

PART IX. THE CYCLIZATION OF SOME NITRO- AND AZIDO-PHENYLPYRIDINES. PYRIDO[1,2-*b*]INDAZOLE[1,2]

R. A. Abramovitch and K. A. H. Adams

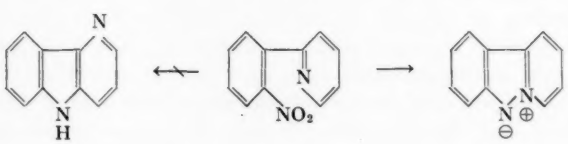
ABSTRACT

Heating 2-*o*-nitrophenylpyridine with ferrous oxalate gives rise to pyrido[1,2-*b*]indazole (III). The evidence for the structure of this compound is discussed. Similarly, heating 2-*o*-nitrophenylpyridine methiodide and *N*-oxide with ferrous oxalate gives (III), in each case, demethylation and deoxygenation preceding the cyclization. In the latter case a minute amount of δ-carboline is also formed. Heating pyridine-*N*-oxides with ferrous oxalate is a potentially general method of effecting deoxygenations of these compounds. Contrary to the results of Smith and Boyer (11), it is found that heating 2-*o*-azidophenylpyridine also gives rise to (III). On the other hand, the action of heat on 2-*o*-azidophenylpyridine-*N*-oxide gives a mixture of δ-carboline and δ-carboline-*py*-*N*-oxide in low yield. The mechanism of the cyclization of the azides and of the reaction taking place on heating nitro-compounds with ferrous oxalate is discussed briefly; the formation of a nitrene intermediate is favored.

The catalytic reduction of 2-*o*-nitrophenylpyridine-*N*-oxide giving rise to the azoxy-, azo-, and hydrazo-derivatives is described and the ultraviolet absorption spectra of these compounds are discussed. It is concluded the steric inhibition of coplanarity exists in the azoxy- and azo-compounds leading to the lack of effective conjugation across the N=N bond.

When this work was initiated no suitable method for the synthesis of the δ-carboline ring system was available. Since that time, however, δ-carboline (I) has been obtained in this laboratory by the thermal cyclization of 3-azido-2-phenylpyridine (1). The yields in this reaction are variable, however, and a better method was sought. To this end, the action of ferrous oxalate on 2-*o*-nitrophenylpyridine was investigated.

Ferrous oxalate has been used in a number of interesting cyclizations. Thus, heating it with 2-nitrodiphenyl gives rise to carbazole (2); phenazines have also been obtained from 2-nitrodiphenylamines by this method (2, 3). On the other hand, 4-nitrocarbazole was not obtained from 2,2′-dinitrodiphenyl, but instead 3,4-benzocinnoline was isolated (2). The action of ferrous oxalate on 2-*o*-nitrophenylpyridine (II) at 300° has now been examined. It was anticipated that the pyridine nuclear carbons might be relatively deactivated towards such a cyclization, but that it could conceivably occur at the 3-position of the pyridine ring to give δ-carboline. Cyclization did, in fact, occur but onto the pyridine nitrogen atom to give pyrido[1,2-*b*]indazole (III), no δ-carboline being formed.



(I) (II) (III)

The evidence for the formulation of the cyclization product as pyrido[1,2-*b*]indazole is as follows:

(i) The product is different from any of the carbolines, all of which are now known,

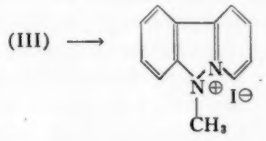
[1]*Manuscript received April 26, 1961.*
Contribution from the Department of Chemistry, University of Saskatchewan, Saskatoon, Saskatchewan. Part of this paper formed the subject of a lecture given at the Fifth Western Regional Conference of the Chemical Institute of Canada held in Regina in September, 1960.
[2]*Part VIII: Can. J. Chem.* **38**, *2152 (1960).*

and melts (83–84°) well below the melting point of the carbolines (~200°). It analyzed correctly for $C_{11}H_8N_2$.

(ii) The infrared spectrum of the compound did not exhibit an N—H stretching absorption and no active hydrogen could be detected. On the other hand, γ-carboline gave an atom of active hydrogen quantitatively. The compound is unaffected by boiling with mineral acids or with aqueous ethanolic alkali (no rearrangement to a more stable structure) and does not take up hydrogen in the presence of Adams' catalyst at atmospheric pressure. It does form an unstable hydrochloride and a picrate.

(iii) Unlike the carbolines, it did not form a methiodide readily, but did so to give (IV) under forcing conditions (in ethanol in a sealed tube for 18 hours at 100°). That no C-alkylation had taken place in this reaction was indicated by the absence of a C—CH_3 group (Kühn-Roth).

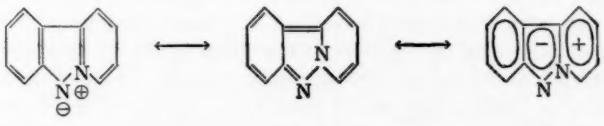
(iv) The infrared spectrum of the product showed a medium intensity band at 1650 cm^{-1}, somewhat higher than is usually found for aromatic rings. A similarly high frequency (1642 cm^{-1}) was reported (4) for anthranil in which a dipolar form —C_6H_4—$\overset{\ominus}{N}$— contributes greatly to the structure. The ultraviolet absorption spectra of (III) and its derivatives are also interesting. The spectrum of the free base in alcohol, that of the



(IV)

base in alcohol at pH 11, and that of the hydrochloride in alcohol are identical, pointing to the dissociation of the hydrochloride in this solvent. On the other hand, the base in aqueous hydrochloric acid at pH 1 had a spectrum very similar to that of the methiodide (IV) in alcohol, the methyl group having its usual bathochromic effect. The most striking features of the latter ultraviolet spectra are the very high extinction coefficients of the low wavelength bands ($\epsilon \times 10^{-3}$ 182.4 and 196.0 for the hydrochloride and methiodide respectively).

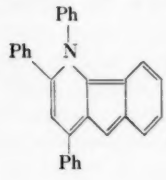
The heterocyclic rings in (III) are isoelectronic with azulene and one could write a number of canonical structures for this molecule:



(A) (B) (C)

A number of lines of evidence point to the fact that the orthoquinonoïd anhydro-base structure (B) is probably a minor contributor to the resonance hybrid. Azulene (in which the dipolar structure plays only a small role), 1,2-benzazulene (V), and a variety to pseudo-azulenes such as 1,2,4-triphenylindeno[1,2-*b*]pyridine (VI) (5) are all highly colored; all the carboline anhydro-bases are deep yellow or orange. Paoloni and Marini-Bettòlo (6) have attributed the color of the anhydronium base of 7-azaindole to the

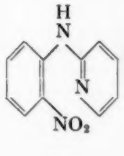
(V)



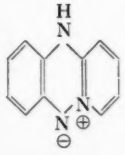
(VI)

orthoquinonoïd form and have suggested that the carboline anhydronium bases as well as sempervirine are best represented by the covalent formulae not bearing separated charges.* From a study of the spectral properties of the δ-carboline anhydronium base Abramovitch, Adams, and Notation (1) suggested that the quinonoïd structure is a more important contributor to the resonance hybrid than the dipolar one. On the other hand, pyrido[1,2-*b*]indazole is colorless, as is its methiodide. In addition, carboline anhydronium bases form *ind-N*-methiodides readily at room temperature (1, 8) whereas (III) only does so under forcing conditions. Similarly, carboline anhydronium bases can be readily hydrogenated (e.g. reduction of cryptolepine (9)) whereas pyrido[1,2-*b*]indazole is not. Gray (10) has interpreted the low base strength of the α-carboline anhydronium base (pK_a 7.75)† as compared with the γ-derivative (pK_a 10.54) on the basis of two factors: (*a*) a much increased stability of the α-anhydronium base as a result of the juxtaposition of the oppositely charged centers (presumably in the dipolar form); and (*b*) a reduced stability of the α-carboline salt owing to the inductive effect of the indole nitrogen attached to the same carbon as the positively charged pyridine nitrogen. It would be expected that in (A) ↔ (C) these effects would be greatly intensified; in fact the pK_a of pyrido[1,2-*b*]indazole has now been found to be approximately 2.48, slightly more than five p*K* units lower than the base strength of the α-carboline anhydronium base!

An attempt was made to obtain further examples of this type of cyclization onto a pyridine nitrogen atom. 2-Nitro-*N*-2′-pyridylaniline (VII) was prepared from 2-bromopyridine and *o*-nitroaniline. The action of ferrous oxalate at 300° on (VII) led to the formation of tars, no product corresponding to (VIII) being detected. This was not totally unexpected since the central ring in (VIII) would be nonaromatic (8 π electrons, compared with 6 π electrons in (III)) so that the incentive leading to its formation may have been lacking. A similar result was obtained using *N*-methyl-2-nitro-*N*-2′-pyridylaniline.



(VII)



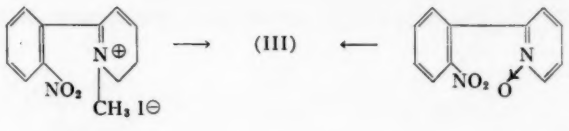
(VIII)

It was hoped to force cyclization to occur at C_3 by blocking the pyridine nitrogen atom

**Paoloni (7) has recently elaborated further on this point. Apart from the fact that his calculations do not lead to correct values for the pK_a and U.V. spectrum of δ-carboline, his conclusion that it is unnecessary to represent the carboline anhydro-bases as hybrids of dipolar and quinonoïd structures in view of the fact that his results "illustrate eloquently the compromise between the tendency to form the (aromatic) sextet and that to neutralize the charges" seems a contradiction in ideas.*

†The pK_a of this compound, as determined by us (1), was 7.55.

in (II). Thus, 2-*o*-nitrophenylpyridine methiodide (IX) and 2-*o*-nitrophenylpyridine-*N*-oxide (X) were prepared. It was realized that the *N*-oxide grouping in (X) might not survive the reducing conditions present during the cyclization reaction but it was hoped that cyclization at the 3-position would occur before reduction. In actual practice, heating either (IX) or (X) with ferrous oxalate led to the formation of pyrido[1,2-*b*]indazole. Chromatography on a column of alumina of the crude product from the cyclization of the *N*-oxide yielded, apart from (III), trace amounts of a solid which had an infrared spectrum almost identical with that of δ-carboline. Insufficient material was available to study this product further.



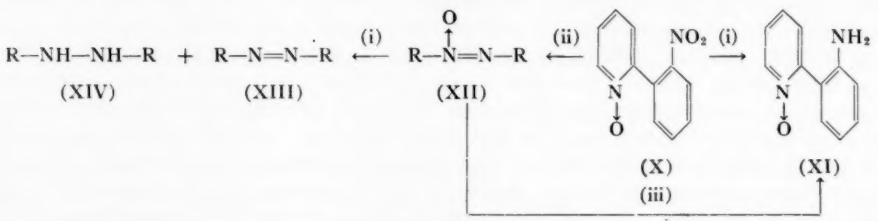
(IX) (X)

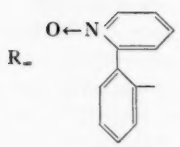
It was of interest from the point of view of the mechanism of the cyclization reaction to determine whether elimination of the protecting groups could occur prior to the cyclization, or whether some mode of concerted attack by the intermediate formed from the reduction of the nitro group and elimination of the protecting group was taking place. To this end, the action of ferrous oxalate at 300° on 2-phenylpyridine methiodide and 2-phenylpyridine-*N*-oxide was studied; in both cases 2-phenylpyridine was isolated in yields comparable to the respective reactions using (IX) and (X). In fact, 2-phenylpyridine could be obtained from the corresponding methiodide by heating it at 300° with granulated lead (used to permit the even distribution of heat in the mixture during such cyclization reactions) but without ferrous oxalate. On the other hand, 2-phenylpyridine-*N*-oxide was recovered unchanged under such conditions. It would, therefore, seem that elimination of the protecting group probably precedes cyclization onto the ring nitrogen atom, though the isolation of a trace of a second product in the *N*-oxide case suggests that conditions might be found where the reverse might be achieved. The reduction of the pyridine-*N*-oxide by ferrous oxalate may well be a general reaction of such amine oxides; this is under investigation.

Smith and Boyer (11) attempted to prepare δ-carboline by the thermal cyclization of 2-*o*-azidophenylpyridine in decalin solution but reported obtaining instead 2-*o*-aminophenylpyridine, formed presumably by hydrogen abstraction from the solvent by the intermediate involved. In the present work this reaction gave rise to a 60% yield of pyrido[1,2-*b*]indazole, only a trace of diazotizable material being detected in the crude reaction mixture. No amine could be isolated by chromatography of the crude product on alumina. Attempts at photodecomposition of the azide in solution were unsuccessful though some darkening did occur. This is similar to the experience of Smolinsky, who was working with 2,4,6-trimethyl-2′-azidodiphenyl (12).

Once again, blocking the pyridine nitrogen atom by *N*-oxide formation prior to cyclization was attempted. 2-*o*-Nitrophenylpyridine-*N*-oxide (X) could be reduced catalytically in acetic acid solution with hydrogen and palladium–charcoal to the amine (XI), the *N*-oxide grouping being unaffected. This result is in agreement with previous hydrogenations of pyridine-*N*-oxides (13, 14) which indicated that the *N*-oxide group in 2-substituted pyridine-*N*-oxides was sterically hindered and thus resisted reduction. If, on the

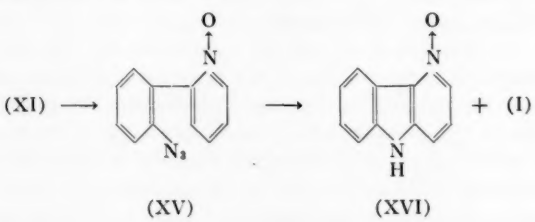
other hand, the catalytic reduction was carried out in alcohol solution the product isolated was 2,2′-di-(*N*-oxido-2-pyridyl)azoxybenzene (XII). This, on catalytic reduction in glacial acetic acid solution gave 2,2′-di-(*N*-oxido-2-pyridyl)azobenzene (λ_{max} 230, 323, 455 mμ; λ_{infl} 260 mμ; $\epsilon \times 10^{-3}$ 44.73, 19.02, 0.58, 28.70) (XIII) together with a small amount of what is probably the hydrazo-compound (XIV), though the latter proved to be very difficult to purify. Its structure was inferred from its infrared spectrum and from its ultraviolet absorption spectrum, which was similar to that of 2-*o*-aminophenylpyridine-*N*-oxide (XI). The azoxy-compound (XII) was reduced directly to the amine (XI) by stannous chloride and hydrochloric acid. These reductions are somewhat similar to those reported by Hayashi, Yamanaka, Iyima, and Matsushita (15), who studied the catalytic reduction of 4,4′-azoxypyridine 1,1′-dioxide. The amine (XI) was converted





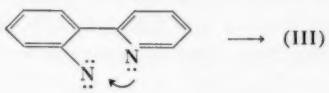
(i) 5% Pd–C in AcOH; (ii) 5% Pd–C in EtOH; (iii) $SnCl_2$–HCl.

to the azide (XV), which, on thermal decomposition in decalin solution, gave a crude mixture from which δ-carboline (I) and δ-carboline-*py*-*N*-oxide (XVI) could be isolated in low yield by chromatography on alumina. The structure of (XVI) was proved by its synthesis from authentic δ-carboline.



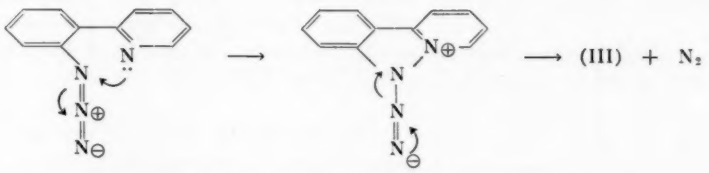
It is interesting to speculate about the mechanisms of the cyclization onto the pyridine nitrogen atom reported here. In the case of the thermal decomposition of the azides two groups of workers have very recently suggested that a nitrene, —N:, may be involved (12, 16). Such an entity, were it formed, would be isoelectronic with a carbene and could be strongly electrophilic. In support of this suggestion is the finding that thermal decomposition of 2,4,6-trimethyl-2′-azidodiphenyl gives rise to 8,10-dimethylphenanthridine (12), which can conceivably arise by attack of a benzylic C—H by a nitrene intermediate.

This may well explain the present results; such an electrophilic species would certainly tend to attack the pair of electrons on the pyridine nitrogen atom rather than the 3-position of the pyridine ring which is deactivated toward electrophilic substitution. On

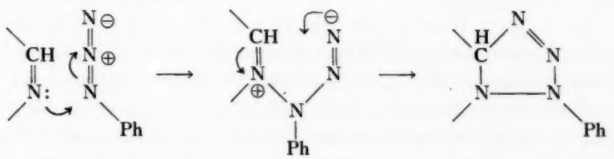


(D)

the other hand, one cannot at present eliminate a concerted or perhaps two-stage mechanism involving cyclization concurrent with, or followed by, the elimination of a nitrogen molecule:



Such a N—N bond formation has an analogy in the known reaction of aryl azides with benzaldehyde arylhydrazones which gives rise to tetrazole derivatives (17) for which one might visualize the following sequence:



We tend to prefer the "nitrene intermediate" mechanism at the present time, at least as far as the reaction leading to (XVI) and (I) goes (for arguments in favor of the formation of such an intermediate see ref. 12). A nitrene intermediate is probably formed during the ferrous oxalate cyclization of the nitro-compounds and it would be attractive to visualize a common reactive intermediate species for both of these reactions, leading as they do to the same product. The concerted mechanism for the conversion of the azide to (III) must, however, be seriously considered.

Not much is known concerning the mode of action of ferrous oxalate in these reactions. It presumably decomposes thermally to give a very reactive form of ferrous oxide (some iron may also be formed), which is the actual reducing agent (2, 3). This can either abstract both oxygen atoms from the nitro-group to give a nitrene (D), or else first give rise to a nitroso-derivative which could then add to the pyridine nitrogen atom and lose a second atom of oxygen to form the pyrido[1,2-*b*]indazole. The latter pathway seems a less likely one in view of the above azide cyclizations.

One further matter should be commented on and that is the similarity between the ultraviolet absorption spectra of the azoxybenzene (XII), the azobenzene (XIII), the hydrazo-derivative (XIV), and the amine (XI) (Fig. 1). The spectra of (XIV) and (XI) are almost superimposable (as expected), except that in the case of (XIV) the

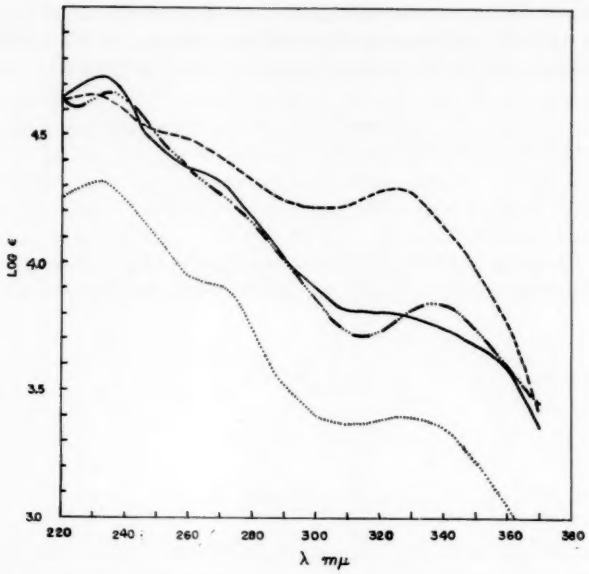


FIG. 1. Ultraviolet absorption spectra in 95% ethanol solution. —— 2,2′-Di-(*N*-oxido-2-pyridyl)azoxybenzene; – – – 2,2′-di-(*N*-oxido-2-pyridyl)azobenzene; —·· 2,2′-di-(*N*-oxido-2-pyridyl)hydrazobenzene; ···· 2-*o*-aminophenylpyridine-*N*-oxide.

maxima have all undergone a small bathochromic shift and the intensities are markedly greater. On the other hand, the spectra of azoxybenzene, azobenzene, and aniline are quite different from each other (18, 19), which is not the case for our compounds. One would have to attribute such a result to steric hindrance in the cases of (XII) and (XIII) preventing coplanarity of the two benzene rings and the N=N linkage and thus inhibiting effective conjugation across that linkage. This would result in each of these molecules having an absorption spectrum similar to that of the amine (XI), only more intense, which is what is actually observed.

EXPERIMENTAL

Melting points are uncorrected. Infrared spectra were measured using a Perkin–Elmer Model 21 instrument equipped with sodium chloride optics. Ultraviolet absorption spectra were measured on a Cary Model 14 recording spectrometer.

Action of Ferrous Oxalate on 2-o-Nitrophenylpyridine–Pyrido[1,2-b]indazole

2-*o*-Nitrophenylpyridine (20) (1 g) and ferrous oxalate dihydrate (1.3 g) were mixed with granulated lead (10 g) and heated at 300° (internal temperature) (metal bath) for 45 minutes. (At the beginning of the reaction the smell of ammonia being evolved could be detected and a piece of red litmus paper held at the mouth of the flask turned blue.) The cooled mixture was extracted repeatedly with ether, and the combined extracts were dried ($MgSO_4$) and evaporated to give an oil which solidified and was recrystallized from light petroleum (b.p. 60–80°) (charcoal) giving *pyrido[1,2-b]indazole* as rods (0.5 g), m.p. 83–84°. Calc. for $C_{11}H_8N_2$: C, 78.57; H, 4.76; N, 16.66; mol. wt. 168. Found: C,

78.47; H, 4.80; N, 16.90; mol. wt. 152. No active hydrogen was present in the product. An active hydrogen determination on γ-carboline gave 0.61% active H (calc. 0.6%). Infrared spectrum (Nujol mull) (main peaks only): 1650 (m), 1623 (m), 749 (s), 743 (s), and 719 cm^{-1} (s). Ultraviolet absorption spectrum (free base in 95% ethanol or base in alcohol at pH 11): λ_{max} 205, 229, 269, 327 mμ; $\epsilon \times 10^{-3}$ 21.0, 32.7, 23.7, 11.8.

When dry hydrogen chloride was passed through an ethereal solution of pyrido[1,2-*b*]-indazole, an impure hydrochloride, m.p. 161–164°, separated which crystallized from ethanol–ether in needles, m.p. 165–166°. Its ultraviolet absorption spectrum in 95% ethanol, however, was identical with that of the free base, indicating that in this solvent the hydrochloride dissociates to the free base. On the other hand, the base in aqueous hydrochloric acid at pH 1 had λ_{max} 208, 254, 330, 340 mμ; $\epsilon \times 10^{-3}$ 182.4, 140.7, 10.02, 11.37.

The approximate pK_a of pyrido[1,2-*b*]indazole, as determined by potentiometric titration (no solvent correction applied), was 2.48.

Pyrido[1,2-b]indazole picrate separated from alcohol and was recrystallized from acetone, giving yellow needles, m.p. 205°. Calc. for $C_{11}H_8N_2,C_6H_3O_7N_3$: C, 51.50; H, 2.77. Found: C, 51.75; H, 3.00.

The free base was recovered unchanged on:

(i) shaking with hydrogen and Adams' catalyst;
(ii) boiling with 10% hydrochloric acid for 4 hours;
(iii) boiling with 20% aqueous ethanolic potassium hydroxide for 6 hours;
(iv) treatment with an excess of methyl iodide in ethanol at room temperature.

9-Methylpyrido[1,2-b]indazolium Iodide

Pyrid[1,2-*b*]indazole (0.2 g) in ethanol (2 ml) was heated with an excess of methyl iodide (2 ml) in a sealed tube at 100° (water bath) for 18 hours. The product which crystallized out on cooling was taken up in ethanol and combined with the mother liquors and the solution was evaporated to a small volume after boiling with charcoal. Brownish plates (0.3 g) separated which were recrystallized from ethanol to give brownish shiny plates, m.p. 208–209°. These were dissolved in water and filtered from a trace of amorphous brown solid, and the filtrate evaporated to dryness to give the *methiodide*, which on recrystallization from ethanol was obtained as cream-colored prisms, m.p. 226–227°. Calc. for $C_{12}H_{11}N_2I$: C, 46.45; H, 3.55; N, 9.03; I, 40.97. Found: C, 46.88; H, 3.66; N, 8.75; I, 40.63. No C—CH_3 was found in a Kühn-Roth determination. λ_{max} 223, 256, 334, 349 mμ; $\epsilon \times 10^{-3}$ 196.0, 20.0, 9.1, 11.8 (in ethanol).

2-Nitro-N-2'-pyridylaniline

2-Bromopyridine (5 g, redistilled), *o*-nitroaniline (6 g), anhydrous potassium carbonate (4.5 g), and a trace of copper-bronze were heated at 195–210° (metal bath) for 7 hours when no more carbon dioxide was evolved. Water was added and the excess *o*-nitroaniline removed by steam distillation. The residue was extracted with chloroform, the extract dried ($MgSO_4$) and evaporated, and the residue vacuum distilled to give *2-nitro-N-2'-pyridylaniline* as a red oil (2.4 g), b.p. 140–150° at 0.05 mm, which solidified. The product could be recrystallized from light petroleum (b.p. 40–60°) and formed red rods, m.p. 68–69°. Calc. for $C_{11}H_9O_2N_3$: C, 61.39; H, 4.22. Found: C, 61.52; H, 4.00.

The *hemipicrate* separated from ethanol and was recrystallized from the same solvent to give yellow plates, m.p. 172°. Calc. for $C_{11}H_9O_2N_3,\frac{1}{2}C_6H_3O_7N_3$: C, 51.0; H, 3.2. Found: C, 51.1; H, 3.1.

2-o-Nitrophenylpyridine-N-oxide

2-*o*-Nitrophenylpyridine (0.9 g) was dissolved in glacial acetic acid (20 ml), and 35% hydrogen peroxide (0.44 g) was added. The solution was heated on a water bath at 90° for 9 hours. An additional amount of 35% hydrogen peroxide (0.44 g) was added and heating was continued at 90° for a further 9 hours. The acetic acid was removed by distillation under reduced pressure and the residue was dissolved in chloroform. Anhydrous sodium carbonate was added to neutralize the remaining acetic acid and the solution was filtered and evaporated to dryness. The residue was crystallized from benzene – light petroleum (b.p. 60–80°) and gave the *N-oxide* (0.92 g) as yellow needles, m.p. 156–157°. Calc. for $C_{11}H_8O_3N_2$: C, 61.11; H, 3.73. Found: C, 61.24; H, 3.75.

1-Methyl-2-o-nitrophenylpyridinium Iodide

2-*o*-Nitrophenylpyridine (0.5 g) in 95% ethanol was treated with an excess of methyl iodide and the solution was allowed to stand at room temperature overnight. On concentration the solution yielded small orange crystals (0.55 g) which were recrystallized from methanol to give the *methiodide* as prisms, m.p. 223–224° (decomp.). Calc. for $C_{12}H_{11}O_2N_2I$: C, 42.08; H, 3.19. Found: C, 42.28; H, 3.30.

Action of Ferrous Oxalate on 2-o-Nitrophenylpyridine-N-oxide

2-*o*-Nitrophenylpyridine-*N*-oxide (1 g), ferrous oxalate dihydrate (1.2 g), and granulated lead (12 g) were intimately mixed and heated at 275–300° (internal temperature) in a metal bath. A small amount of strong-smelling gas which was basic to litmus was evolved during the heating period. The cooled mixture was extracted repeatedly with ether and then with hot benzene. The combined extracts were dried (Na_2SO_4) and evaporated to dryness to yield a brown oil (0.22 g) which was chromatographed on neutral alumina. Elution with benzene gave a light brown crystalline compound (0.19 g) which could be recrystallized from light petroleum (b.p. 60–80°) and had m.p. 84–86°. The infrared spectrum of this product was identical with that of an authentic sample of pyrido[1,2-*b*]indazole. The melting point of the base and its picrate were undepressed on admixture with authentic samples. Elution with benzene–ether yielded a tan solid (0.005 g), m.p. 202–205°, the infrared spectrum of which was almost identical with that of δ-carboline.

Action of Ferrous Oxalate on 1-Methyl-2-o-Nitrophenylpyridinium Iodide

1-Methyl-2-*o*-nitrophenylpyridinium iodide (0.6 g) was intimately mixed with ferrous oxalate dihydrate (0.7 g) and granulated lead (6 g). The mixture was heated at 275–300° (internal temperature) in a metal bath for 30 minutes. A small amount of a strong-smelling, basic (litmus) gas was evolved during the heating period. The reaction mixture was cooled and the black residue was repeatedly extracted with ether. The combined ether extracts were dried (Na_2SO_4) and evaporated to give a brown oil (0.1 g) which partly solidified. This product was recrystallized from light petroleum (b.p. 60–80°) giving tan crystals (0.078 g) which proved to be identical with pyrido[1,2-*b*]indazole (mixed melting point, infrared spectrum).

Cyclization of 2-o-Azidophenylpyridine

2-*o*-Azidophenylpyridine (11) (1.2 g, not purified) was dissolved in redistilled decalin (50 ml) and the solution was heated in an oil bath at 160–170° (internal temperature). Gas bubbles began to be evolved smoothly at about 140°. After 10–15 minutes when no more gas evolution could be observed, the solution was cooled and was extracted with 10% hydrochloric acid. The acid extract was washed with ether, basified with 2 *N*

sodium hydroxide, and extracted repeatedly with ether. The combined ether extracts were dried (Na_2SO_4) and evaporated to give an oil which solidified. Recrystallization from light petroleum (b.p. 60–80°) gave pyrido[1,2-*b*]indazole (0.54 g), m.p. 84.5–85.5°. The melting point was not depressed on admixture with an authentic sample. The picrate, m.p. 199–200°, did not depress the melting point of an authentic sample of pyrido[1,2-*b*]indazole picrate. The infrared spectrum of the base was identical with that of an authentic specimen.

No primary amine could be isolated when the crude reaction product was chromatographed on a column of neutral alumina.

2-o-Aminophenylpyridine-N-oxide

2-*o*-Nitrophenylpyridine-*N*-oxide (0.5 g) was dissolved in glacial acetic acid (25 ml) and hydrogenated at atmospheric pressure in the presence of 5% palladium on charcoal (0.1 g). Three molar equivalents of hydrogen were absorbed in less than 1 hour. The catalyst was removed by filtration and washed with a little acetic acid and methanol. The combined filtrates were evaporated under reduced pressure and the residue dissolved in chloroform and treated with anhydrous sodium carbonate. The filtered solution was evaporated to give an oil (0.42 g) which crystallized on trituration with methanol and was recrystallized from methanol to give the *amine* as white crystals, m.p. 181.5–182.5°. Calc. for $C_{11}H_{10}ON_2$: C, 70.95; H, 5.41. Found: C, 70.72; H, 5.38. λ_{max} 232, 325 mμ; λ_{infl} 270, 220 mμ; $\epsilon \times 10^{-3}$ 20.86, 2.54, 8.06, 17.60 (in 95% ethanol).

2-o-Azidophenylpyridine-N-oxide

2-*o*-Aminophenylpyridine-*N*-oxide (0.30 g) was dissolved in concentrated hydrochloric acid (0.6 ml) and water (1.5 ml) and the solution treated at 0° with a solution of sodium nitrite (0.12 g) in water (1 ml). An excess of a saturated aqueous solution of sodium azide was added, the temperature being maintained between 0 and 5°. The white *azide* which precipitated was filtered, washed with water, and dried. The aqueous filtrate was basified with 2 *N* sodium hydroxide, extracted with chloroform, and the extract dried (Na_2SO_4). Evaporation of the chloroform yielded an additional quantity of azide. The combined solid products (0.286 g) were recrystallized from benzene – light petroleum (b.p. 60–80°) and had m.p. 165–166°. Calc. for $C_{11}H_8ON_4$: C, 62.25; H, 3.80. Found: C, 62.60; H, 3.88.

Cyclization of 2-o-Azidophenylpyridine-N-oxide

2-*o*-Azidophenylpyridine-*N*-oxide (0.5 g) was dissolved in hot redistilled decalin (60 ml) and the solution heated in an oil bath at 175–180° (internal temperature) for 40 minutes during which time nitrogen was evolved and the solution became very dark. It was then boiled under reflux for an additional 10 minutes, cooled, and the solid which separated was filtered. The decalin solution was extracted with 10% hydrochloric acid, and the aqueous solution was basified with 2 *N* sodium hydroxide and extracted with chloroform. The dried (Na_2SO_4) chloroform extract was evaporated under reduced pressure. The residue was combined with the solid which was filtered off after the reaction (total 0.3 g), dissolved in methanol, filtered to remove some black solid (0.150 g), and the filtrate chromatographed on neutral alumina. Elution with benzene gave a solid (0.010 g) which was identified as δ-carboline by its infrared spectrum and mixed melting point with an authentic specimen. Elution with ether–methanol yielded at first a solid (0.046 g) which could be crystallized from benzene containing a small amount of methanol and had m.p. 277–278° (decomp.). Its infrared spectrum was identical

with that of an authentic sample of δ-carboline-*py*-*N*-oxide and the melting point was not depressed on admixture with a sample prepared from δ-carboline as described below. Subsequent fractions yielded only intractable dark brown residues.

δ-Carboline-py-N-oxide

δ-Carboline (0.050 g) was dissolved in glacial acetic acid (8 ml), and 35% hydrogen peroxide (0.1 g) was added. The solution was heated on a water bath at 90° for 10 hours. More 35% hydrogen peroxide (0.1 g) was added and heating was continued for an additional 9 hours. The acetic acid was evaporated under reduced pressure, and the residue was dissolved in chloroform and treated with anhydrous sodium carbonate. Evaporation of the chloroform gave the *N-oxide* (0.050 g) which was recrystallized from benzene containing some methanol (charcoal). This crude yellow product was dissolved in dilute hydrochloric acid, filtered, basified with 2 *N* sodium hydroxide, and extracted with chloroform. Evaporation of the dried (Na_2SO_4) chloroform solution gave a white residue which was recrystallized from benzene containing some methanol to give white crystals which melted at 277–278° (decomp.). Calc. for $C_{11}H_8N_2O$: C, 71.72; H, 4.38. Found: C, 71.65; H, 4.60. Infrared spectrum (KBr disk) (main peaks only): 1630 (m), 1605 (m), 1574 (m), 1215 (s), 865 (m), 782 (m), 750 (s), 705 cm^{-1} (s).

Catalytic Reduction of 2-o-Nitrophenylpyridine-N-oxide in 95% Ethanol – 2,2′-Di-(N-oxido-2-pyridyl)azoxybenzene

2-*o*-Nitrophenylpyridine-*N*-oxide (0.82 g) was dissolved in 95% ethanol (35 ml) and hydrogenated at atmospheric pressure in the presence of 5% palladium on charcoal (0.17 g). The reduction was complete in about 90 minutes. The catalyst was filtered and washed with glacial acetic acid. The combined filtrates were evaporated to a small volume under reduced pressure, the residue was dissolved in chloroform and treated with anhydrous sodium carbonate to neutralize any remaining acetic acid. The solution was filtered and evaporated to dryness and the residue recrystallized from methanol to give the *azoxy* compound (0.58 g), m.p. 236–237°. Calc. for $C_{22}H_{16}O_3N_4$: C, 68.74; H, 4.38. Found: C, 68.46; H, 4.32. Infrared spectrum (KBr disk) (main peaks only): 1600 (m), 1255 (s), 850 (s), 780 (s), 770 (s), 750 cm^{-1} (sh). λ_{max} 233, 325 mμ; λ_{infl} 220, 270 mμ; $\epsilon \times 10^{-3}$ 53.50, 6.50, 43.20, 21.00 (in 95% ethanol).

Catalytic Reduction of 2,2′-Di-(N-oxido-2-pyridyl)azoxybenzene in Glacial Acetic Acid – 2,2′-Di(N-oxido-2-pyridyl)azobenzene and 2,2′-Di-(N-oxido-2-pyridyl)hydrazobenzene

2,2′-Di-(*N*-oxido-2-pyridyl)azoxybenzene (0.050 g) was dissolved in glacial acetic acid (10 ml) and hydrogenated at atmospheric pressure in the presence of 5% palladium on charcoal (0.010 g). The reduction product was isolated as in the previous experiment. The residue was washed with methanol and crystallization took place. The crude product was separated by fractional crystallization from benzene into *2,2′-di-(N-oxido-2-pyridyl)-azobenzene* obtained as orange crystals (0.020 g), m.p. 264° (decomp.) [Calc. for $C_{22}H_{16}O_2N_4$: C, 71.72; H, 4.38. Found: C, 71.62; H, 4.71. Infrared spectrum (KBr disk) (main peaks only): 1585 (w), 1255 (s), 845 (s), 780 (s), 750 cm^{-1} (m). λ_{max} 230, 323, 455 mμ; λ_{infl} 260 mμ; $\epsilon \times 10^{-3}$ 44.73, 19.20, 0.58, 28.70 (in 95% ethanol)], and 2,2′-di-(*N*-oxido-2-pyridyl)hydrazobenzene (0.018 g), obtained as a white solid which, because of its insolubility, was very difficult to purify, m.p. 225° (decomp.). Infrared spectrum (KBr disk) (main peaks only): 3350 (m), 1595 (s), 1247 (s), 842 (s), 780 (m), 750 cm^{-1} (s). λ_{max} 236, 338 mμ; λ_{infl} 265 mμ; $\epsilon \times 10^{-3}$ 46.70, 6.88, 21.15 (in 95% ethanol).

Reduction of 2,2'-Di-(N-oxido-2-pyridyl)azoxybenzene with Stannous Chloride – 2-o-Aminophenylpyridine-N-oxide

2,2'-Di-(*N*-oxido-2-pyridyl)azoxybenzene (0.113 g) dissolved in concentrated hydrochloric acid (3 ml) was treated with a solution of stannous chloride dihydrate (0.24 g) in concentrated hydrochloric acid (1 ml). The solution was heated on the steam bath for 90 minutes. The cooled reaction mixture was basified with 2 *N* sodium hydroxide and extracted with ether. The dried (Na_2SO_4) ether solution was evaporated to give the primary amine (0.090 g) which was recrystallized from methanol–ether and had m.p. 179–181°. The melting point was not depressed on admixture with an authentic sample of 2-*o*-aminophenylpyridine-*N*-oxide and the infrared spectra of the two samples were identical.

2-Phenylpyridine Methiodide

2-Phenylpyridine and an excess of methyl iodide were kept at room temperature for 2 days in the absence of light. The *methiodide* which separated was recrystallized from ethyl acetate – methanol to give colorless needles, m.p. 143–144°. Calc. for $C_{12}H_{12}NI$: C, 48.50; H, 4.06. Found: C, 48.61; H, 4.25.

Demethylation of 2-Phenylpyridine Methiodide

(a) With Ferrous Oxalate

The methiodide (0.14 g) was mixed with ferrous oxalate dihydrate (0.16 g) and granulated lead (2 g) and the mixture heated in a metal bath at 290–300° under an air condenser for 30 minutes. The cooled reaction mixture and condensate were extracted with ether, and the ether layer was washed with sodium thiosulphate solution to remove iodine and dried (Na_2SO_4). Evaporation of the ether gave 2-phenylpyridine (0.037 g, 50%), picrate, m.p. 172–173°, undepressed on admixture with an authentic specimen.

(b) Without Ferrous Oxalate

The procedure was exactly as under (*a*) except that no ferrous oxalate was added. 2-Phenylpyridine (74% yield) was isolated.

Action of Ferrous Oxalate on 2-Phenylpyridine-N-oxide

2-Phenylpyridine-*N*-oxide (0.30 g) (21) was mixed with ferrous oxalate dihydrate (0.40 g) and granulated lead (4 g) and treated as for the methiodide reaction. 2-Phenylpyridine (0.171 g, 63%), b.p. 132–134° at 10 mm, picrate, m.p. 172–173°, undepressed on admixture with an authentic specimen, was thus obtained.

When ferrous oxalate was omitted, the starting *N*-oxide was recovered.

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OXIDATION–REDUCTION POLYMERS

I. SYNTHESIS OF MONOMERS[1]

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ABSTRACT

The preparation of two new monomers, 2,5-bis-(2-tetrahydropyranyloxy)-4′-vinyldiphenyl sulphone and 2-tetrahydropyranyl-4′-vinylphenyl thioether, for the synthesis of redox polymers is described.

The first systematic discussion of redox (electron exchange) polymers was presented by Cassidy (1). These polymers were divided into two classes: (i) those in which the active redox group formed a part of the backbone of the polymer chain and (ii) those in which the active group was a substituent on the polymeric chain. Examples of the first class are various condensation resins of hydroquinones, naphthaquinones, and anthraquinones with phenol and formaldehyde (2–6).

Polyvinylhydroquinone (7) is an example of the second class. Monomers such as vinylhydroquinone dibenzoate (8) and diacetate (8, 9) were produced, since it was soon realized that in order to obtain high molecular weight polymers, the hydroxyl groups in the monomer should be protected. Other vinyl monomers were synthesized, such as vinylhydroquinone bis-methoxymethyl ether (10), 1-vinyl-2,4,5-trimethyl-3,6-dihydroxybenzene (11), β-vinylanthraquinone (12, 13), and 2-methyl-3-vinyl-1,4-naphthaquinone (14). A polyhydroquinone was prepared from 3-(2,5-diacetoxyphenyl) propylene oxide (15).

Redox polymers of the second class have also been prepared by reactions with polymers. For example, polyaminostyrene was first diazotized and then reacted with an alcoholic solution of *p*-benzoquinone or 1,4-naphthaquinone (16, 17). Polyaminostyrene was also reacted directly with a naphthaquinone (16). Polyvinyl alcohol was reacted with β-formylanthraquinone (18).

Polymers of known and easily varied structure have obvious advantages in any systematic study of the properties of redox polymers. Our efforts have therefore been directed towards the synthesis of a vinyl monomer for which the oxidation potential could be varied in a simple manner. This was accomplished by joining a hydroquinone group through a stable sulphone bridge with another benzene ring containing $-CH_2CH_2Br$ side chain. The latter can easily be dehydrobrominated to give a vinyl group. A simple hydroquinone could be replaced by a substituted hydroquinone or a naphthahydroquinone. In this way, different redox polymers could be prepared and their oxidation potentials measured and compared with simple homologues.

Vinyl monomers, reported so far, have generally one property in common: the vinyl group is attached directly to the same benzenoid ring which undergoes a redox cycle. It is possible that the interactions between adjacent redox residues will be different from those of a simple polyvinylhydroquinone (1, 7), since the redox group in the monomer reported here is further removed from the backbone chain.

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Contribution from the Department of Chemical Engineering, University of Toronto, Toronto, Ontario. Taken from the theses submitted by J. Yannopoulos and W. Metanomski to the School of Graduate Studies, University of Toronto in partial fulfillment of the requirements for the degree of Master of Applied Science in May and January, 1960, respectively.
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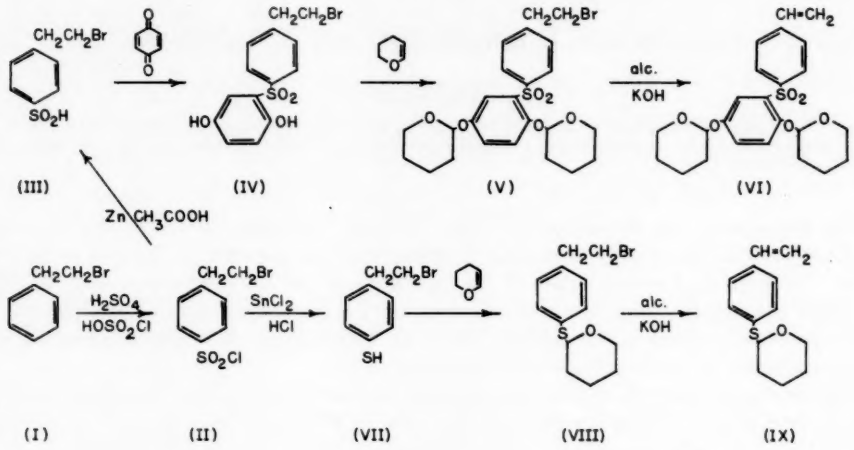
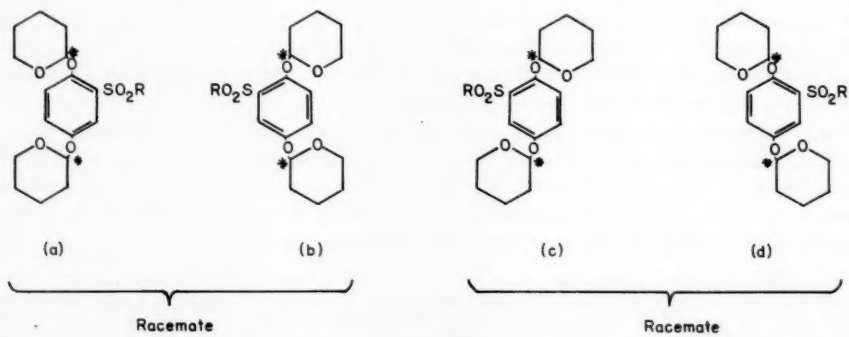
The synthesis of a new monomer, 2,5-bis-(2-tetrahydropyranyloxy)-4′-vinyldiphenyl sulphone (VI) was achieved in five steps according to the scheme shown below.



β-Bromoethylbenzene (I) was chlorosulphonated and then reduced by zinc in acetic acid to *p*-(β-bromoethyl) benzenesulphinic acid (III). The sulphinic acid was reacted with *p*-benzoquinone to give a diphenyl sulphone IV. The hydroxyl groups were protected by making use of a reaction with 2,3-dihydropyran (19) to give a bis-tetrahydropyranyl ether V. Finally, the side chain was dehydrobrominated using an alcoholic solution of potassium hydroxide.

The possibility of the existence of two racemic diastereoisomers of V has not been overlooked. Stern, English, and Cassidy (20) isolated two isomers of bis-2-tetrahydropyranyl ether of hydroquinone, assigning to them the meso and racemic configurations. In our case none of the isomers has a plane of symmetry because of the presence of an additional substituent group —SO_2R, and therefore two racemic diastereoisomers are expected, as shown below.



R = $C_6H_4CH_2CH_2Br$

The hydroxyl groups could also be protected by acetylation or benzoylation, but the esters partially decomposed during dehydrobromination. Dehydrobromination of these esters using other bases, such as pyridine, lutidine, or triethanolamine, is being studied and shows some promise.

The acetal bond, on the other hand, is very stable under strong alkaline conditions. The tetrahydropyranyl groups can be removed from the polymers by an acid treatment, exposing free —OH groups.

Polymers with thiol groups are of interest as another type of redox resin and ion exchanger. Brubaker (21) has patented the synthesis of polyvinylthioacetate and pointed out the oxidation of polyvinylthiol to polyvinyldisulphide. Polythiolstyrene was prepared by Gregor, Dolar, and Hoeschele (22), and Seifert (23) by various reactions on the benzene ring of the polystyrene. Similarly, poly(vinylbenzylmercaptan) was prepared by Parrish (24), Okawara, Nakagawa, and Imoto (25), and Trostyanskaya and Tevlina (26). Hamamura, Tatsukawa, and Uno (27) produced polythiol resins by the condensation of various thiophenols with formaldehyde. Overberger and Lebovits (28) were the first to synthesize a monomer, *p*-vinylphenyl thioacetate, which was polymerized and saponified to give poly-*p*-thiolstyrene.

A new monomer, 2-tetrahydropyranyl-4′-vinylphenyl thioether (IX) was prepared according to the scheme shown above. *p*-(β-Bromoethyl)benzenesulphonyl chloride (II) was reduced to *p*-(β-bromoethyl)thiophenol (VII). This reduction presented some difficulty since with reducing agents evolving hydrogen *in situ*, such as zinc in acidic medium, or lithium aluminum hydride (in the presence of sulphonyl group (29)), there was a simultaneous reduction of both $—SO_2Cl$ and $—CH_2CH_2Br$ groups. The final product of such a reduction was *p*-ethylthiophenol or a mixture of the sulphinic acid III and *p*-ethylthiophenol. The successful reduction of II to VII was achieved by using stannous chloride and hydrogen chloride in acetic acid, in which case no hydrogen was evolved. The thiol group can add across an olefinic bond (28) and therefore this group must be protected before dehydrobromination. Pyranylation with 2,3-dihydropyran has been used for this purpose. After the polymerization tetrahydropyranyl groups can be removed by acid treatment, exposing free —SH groups.

Both monomers were polymerized and copolymerized with other monomers. After acid treatment the polymers exhibited the expected redox properties and, in addition, the polymers with thiol groups had a high affinity for metal cations. A redox membrane was produced and preliminary experiments indicated the transfer of "oxidizing power" through the membrane with an apparent diffusion coefficient of about 5×10^{-7} cm²/second. Investigation of the properties of these redox polymers in bead and membrane form is now in progress.

EXPERIMENTAL*

p-(β-Bromoethyl)benzenesulphonyl Chloride (II)

This compound has been previously prepared by Spinner, Ciric, and Graydon (30). The present procedure is based on the modifications introduced by Worsley (31).

A solution of β-bromoethylbenzene (I) (185 g, 1 mole) and acetonitrile (82 g, 2 moles) was added dropwise to 30% fuming sulphuric acid (265 g) at 20–30°. To the reaction mixture, chlorosulphonic acid (290 g, 2.5 mole) was added, the temperature being kept at 40–45°. Stirring was continued for 1 hour at the same temperature range. The mixture

**Melting points are corrected. Microanalyses were done by Micro-Tech Laboratories, Skokie, Illinois, and Galbraith Laboratories, Inc., Knoxville, Tenn.*

was poured onto crushed ice and allowed to stand in a refrigerator for 30 minutes. The precipitate was filtered and recrystallized from petroleum ether (boiling range 80–100°), yielding 220 g (78%), m.p. 54–54.5° (previously reported 54–55° (30)).

Infrared spectrum: 1179 (s) and 1383 (s) (—SO_2—) cm^{-1} (32).

p-(β-Bromoethyl)benzenesulphinic Acid (III)

The sulphonyl chloride II (50 g, 0.177 mole) was dissolved in glacial acetic acid (250 ml) at room temperature and zinc dust (15 g, 0.23 mole) was added in small portions with constant stirring. The temperature was kept at 25–35°. After 1 hour of additional stirring at 30–35°, concentrated hydrochloric acid (150 ml) and then distilled water (125 ml) were added slowly. The reaction mixture was heated to 80°. On cooling of the mixture in an ice bath a white precipitate formed which, recrystallized from hot water, gave 32.5 g (74%) of a product melting at 95–95.5°. The compound changed rapidly on drying (over 1 hour) (33), on standing, and on further recrystallization, as was evidenced by widely varying melting points. Thus, all attempts to provide a sample suitable for analysis failed.

Reduction of the sulphinic acid III with stannous chloride in glacial acetic acid saturated with hydrogen chloride gave *p*-(β-bromoethyl)thiophenol (VII), a product identical with that produced by a direct reduction of the sulphonyl chloride II, as reported below. B.p. 92.5–93°/1.2 mm. Anal. Calc. for C_8H_9BrS (217.13): C, 44.25; H, 4.18; Br, 36.80; S, 14.76. Found: C, 45.05; H, 4.72; Br, 36.28; S, 14.43%.

2,5-Dihydroxy-4′-(β-bromoethyl)diphenyl Sulphone (IV)

This reaction is based on 1,4 addition of an aromatic sulphinic acid to a quinone, first reported by Hinsberg (34).

After many trials with solutions in various solvents, the following procedure, which yielded best results, was adopted. A suspension of *p*-benzoquinone (13.5 g, 0.125 mole) in water (500 ml) was added slowly to a suspension of the sulphinic acid III (31 g, 0.125 mole) in water (1 liter) at room temperature. A gradual change in the consistency of the suspended solid took place, the final product being very fluffy. The typical yellow color of quinone disappeared. Crystallization from 25% (by volume) ethanol gave a light sandy powder (36 g, 81%) melting at 130–130.5°. Anal. Calc. for $C_{14}H_{13}BrO_4S$ (357.22): C, 47.07; H, 3.67; Br, 22.37; S, 8.97. Found: C, 47.26; H, 3.81; Br, 22.61; S, 9.01%. Infrared spectrum: 1152 (s) and 1302 (s) (—SO_2—) (32), 3390 (s) (—OH) cm^{-1}.

A derivative, 2,5-diacetoxy-4′-(β-bromoethyl)diphenyl sulphone, was prepared by reacting the dihydroxysulphone IV with acetic anhydride and a drop of concentrated sulphuric acid as a catalyst. Crystallization from 50% (by volume) ethanol gave a white product melting at 110–110.5°. Anal. Calc. for $C_{18}H_{17}BrO_6S$ (441.30): C, 48.99; H, 3.88; Br, 18.11; S, 7.27. Found: C, 49.33; H, 3.96; Br, 18.25; S, 7.31%. Infrared spectrum: 1153 (s) and 1324 (s) (—SO_2—) (32), —OH band absent.

Another derivative, 2,5-benzoquinone-4′-(β-bromoethyl)phenyl sulphone, was prepared by oxidizing the dihydroxysulphone IV with silver oxide. Orange needles precipitated by high boiling point petroleum ether from a diethyl ether solution melted at 104–104.5°. Anal. Calc. for $C_{14}H_{11}BrO_4S$ (355.21): C, 47.33; H, 3.12; Br, 22.50; S, 9.03. Found: C, 47.10; H, 3.15; Br, 22.94; S, 9.20%.

2,5-Bis-(2-tetrahydropyranyloxy)-4′-(β-bromoethyl)diphenyl Sulphone (V)

The dihydroxysulphone IV (10 g, 0.028 mole) was dissolved in 2,3-dihydropyran (15 g, 0.178 mole) containing a few milligrams of *p*-toluenesulphonic acid as a catalyst. The solution was stirred at room temperature for 2 hours and left at the same temperature

overnight. The volatile materials were then removed under vacuum, and the solid residue taken up in chloroform – diethyl ether (5:2) mixture (150 ml). The solution was shaken with several portions of 5% sodium hydroxide solution to remove the unreacted IV, washed with water, dried over anhydrous sodium sulphate, and concentrated. The precipitate formed was filtered and crystallization from 70% (by volume) ethanol gave 9.8 g (67%) of white crystals melting at 133–134°. Anal. Calc. for $C_{24}H_{29}BrO_6S$ (525.45): C, 54.86; H, 5.56; Br, 15.21; S, 6.10. Found: C, 55.05; H, 5.68; Br, 14.98; S, 5.97%.

This solid is one of the two racemates mentioned in the earlier discussion. Attempts to recover a presumably lower melting and more soluble racemate from the chloroform–ether mother liquor were not successful.

The pyranylated sulphone V decomposed on treatment with hydrochloric acid, giving the dihydroxysulphone IV, melting at 130–131°. This product gave no depression in mixed melting point with the original IV. The other decomposition product was 5-hydroxypentanal, identified by its 2,4-dinitrophenylhydrazone melting at 108.5–109° (reported m.p. 109° (35)).

2,5-Bis-(2-tetrahydropyranyloxy)-4′-vinyldiphenyl Sulphone (VI)

A 10% alcoholic solution of potassium hydroxide (1.6 g KOH, 0.028 mole) was added dropwise to a boiling solution of the diphenyl sulphone V (12 g, 0.023 mole) in benzene (150 ml). The mixture was refluxed on a steam bath for 30 minutes. The precipitated potassium bromide was removed by filtration and the filtrate evaporated to dryness *in vacuo* at room temperature. The residue after a thorough washing with water was crystallized from 50% (by volume) ethanol. The white crystals obtained (6.5 g, 64%) melted at 126.5–127°. Anal. Calc. for $C_{24}H_{28}O_6S$ (444.52): C, 64.84; H, 6.35; S, 7.21. Found: C, 64.67; H, 6.43; S, 7.25; C, 64.60; H, 6.44; S, 7.35%.

p-(β-Bromoethyl)thiophenol (VII)

p-(β-Bromoethyl)benzenesulphonyl chloride (II) was reduced to VII with stannous chloride and hydrogen chloride (36, 37).

Dry hydrogen chloride was bubbled into a suspension of stannous chloride dihydrate (203.5 g, 0.9 mole) in glacial acetic acid (800 ml) at room temperature until the suspension became clear and homogeneous; 71.5 g (1.96 mole) of hydrogen chloride was required. *p*-(β-Bromoethyl)benzenesulphonyl chloride (II) (42.5 g, 0.15 mole) was added and the mixture was shaken for 15 minutes. Evolution of heat was observed during the reaction. On shaking of the mixture with 1:1 hydrochloric acid, a yellowish oil settled. This oil was separated and washed with concentrated hydrochloric acid and then water. Distillation under reduced pressure gave 26.4 g (81%) of a colorless oil* (b.p. 92.5–93°/1.2 mm). Anal. Calc. for C_8H_9BrS (217.13): C, 44.25; H, 4.18; Br, 36.80; S, 14.76. Found: C, 44.53; H, 4.36; Br, 36.76; S, 14.91%.

A derivative, mercuric mercaptide of *p*-(β-bromoethyl)thiophenol, was prepared by adding an excess of 20% mercuric acetate solution in dilute acetic acid to the thiophenol VII. Crystallization from benzene gave snow white crystals melting at 115.5–116.5°. Anal. Calc. for $C_{16}H_{16}Br_2HgS_2$ (632.86): C, 30.36; H, 2.55; Br, 25.26; Hg, 31.70; S, 10.13. Found: C, 30.63; H, 2.67; Br, 25.37; Hg, 31.25; S, 10.33%.

Another derivative, *p*-(β-bromoethyl)phenyl thiobenzoate was prepared by reacting the thiophenol VII with benzoyl chloride dissolved in benzene in the presence of pyridine. Crystallization from ethanol gave white needles, m.p. 49–49.5°. Anal. Calc. for

**This thiophenol (as well as p-ethylthiophenol) was found to be a very strong skin irritant, a well-known property of thiophenols (38).*

$C_{15}H_{13}BrOS$ (321.23): C, 56.08; H, 4.08; Br, 24.88; S, 9.98. Found: C, 56.29; H, 4.70; Br, 24.90; S, 9.74%.

2-Tetrahydropyranyl-4'-(β-bromoethyl)phenyl Thioether (VIII)

The procedure is based on a method of Parham and DeLaitsch (19).

The thiophenol VII (26.3 g, 0.12 mole) was mixed with a 65% excess of 2,3-dihydropyran (27 g, 0.32 mole), 1 ml of ethereal solution of HCl (0.002 mole) was added, and the mixture refluxed for 48 hours at 30°. The mixture was shaken with three portions of 5% sodium hydroxide solution and washed with water. The excess of dihydropyran was removed by evaporation under reduced pressure. Attempts to purify the thioether VIII by distillation were unsuccessful because of its high boiling point and the instability of the brominated side chain at high temperatures.

2-Tetrahydropyranyl-4'-vinylphenyl Thioether (IX)

Approximately 30% excess of 10% alcoholic solution of potassium hydroxide was added to the crude thioether VIII. The mixture was refluxed for 30 minutes. The precipitated potassium bromide was removed by filtration, the filtrate was washed with water, dried over anhydrous sodium sulphate, and distilled under reduced pressure. Traces of *p-tert*-butylcatechol were added as a polymerization inhibitor prior to drying and distillation. The product was a colorless viscous oil (b.p. 134–135°/1.35 mm). Bromination calculated for 1.000 double bond; found 0.998. Anal. Calc. for $C_{13}H_{16}OS$ (220.33): C, 70.86; H, 7.32; S, 14.56. Found: C, 70.86; H, 7.52; S, 13.51; C, 71.72 ; H, 7.70; S, 15.02%.

ACKNOWLEDGMENTS

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PREFERRED RESIDENCE CONFORMATIONS OF DIASTEREOISOMERIC α-β AMINO ALCOHOLS: AN N.M.R. STUDY OF THE EPHEDRINES[1]

J. B. HYNE

ABSTRACT

Nuclear magnetic resonance spectral results including chemical shifts, anisotropy effects, spin coupling constants, and hydrogen bonding phenomena are presented for the diastereoisomeric pair of α-β amino alcohols (−)-ephedrine and (+)-ψ-ephedrine. The results are shown to be in keeping with the existence of a preferred residence conformation for each of the diastereoisomers.

INTRODUCTION

In a recent paper (1) the effect of dilution on the chemical shift associated with the nuclear magnetic resonance of the OH and NH protons of both (+)-ψ-ephedrine and (−)-ephedrine in chloroform solution was reported. This effect, together with a considerable volume of previously available data, was interpreted as evidence for preferred intramolecular hydrogen bonding in the (+)-ψ-ephedrine diastereoisomer compared with (−)-ephedrine. The conclusion was drawn from the assembled evidence that there is a greater probability in the (+)-ψ-ephedrine case of residence in the conformation which permits intramolecular hydrogen bonding than in the (−)-ephedrine case. In summary, (+)-ψ-ephedrine tends to adopt that conformation in which the OH and NH functions have a gauche relationship while (−)-ephedrine shows no such preference.

Freudenberg and co-workers (2) early established the relative configuration of the two asymmetric centers in the ephedrine molecule and found that the two representatives of the diastereoisomeric pairs, (−)-ephedrine and (+)-ψ-ephedrine, differed only in the configuration about the carbon center carrying the hydroxyl group. Assuming, as a first approximation, that the staggered conformations, generated by rotation of the two halves of the molecule about the central carbon–carbon bond, will be the more stable, a set of staggered conformers for the two diastereoisomers can be drawn as shown in Fig. 1. Considering these possible conformations in the light of the hydrogen-bonding evidence (1) it would appear that conformations (*a*) or (*b*) would be the most favored for (+)-ψ-ephedrine since the hydroxyl and methylamino groups are favorably placed for intramolecular hydrogen bonding in these conformers. Since (−)-ephedrine showed no marked tendency toward intramolecular hydrogen bonding, conformer (*y*), with trans disposition of hydroxyl and methylamino groups, must be at least equally favored in conformer population. In an earlier paper on the dissociation constants of the ephedrinium ions Everett and Hyne (3) favored conformers (*a*) and (*y*) for the diastereoisomeric pair on the basis of approximate calculations of repulsive interactions between non-bonded atoms on the adjacent carbon centers.

Recent work (4, 5, 6) on the variation of spin-coupling constants with the dihedral angle between adjacent carbon–hydrogen bonds in ethanic systems suggested the application of this method to the diastereoisomeric ephedrine pair. Figure 1 shows clearly that the dihedral angle between the carbon–hydrogen bond on the hydroxyl center and the carbon–hydrogen bond on the methylamino center varies significantly from one possible conformation to another.

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Contribution from the Department of Chemistry, University of Alberta, Calgary, Calgary, Alberta.

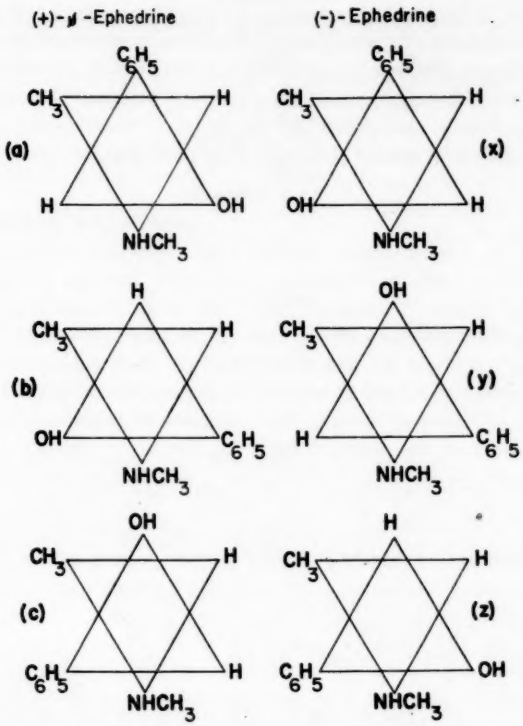

FIG. 1. Possible "pure staggered" conformations of the diastereoisomeric ephedrines.

EXPERIMENTAL

Nuclear magnetic resonance spectra were measured on a Varian V 4300 spectrometer operating at a fixed frequency of 40 Mc; 1.5 molar solutions of BDH (+)-ψ-ephedrine and (−)-ephedrine were prepared in chloroform; the (±)-ψ-ephedrine was used without further purification while the (−)-ephedrine was vacuum-distilled to remove water of hydration. Temperature in the n.m.r. 5-mm spinning sample tube was 20°±1° C throughout. The spectra were scaled by the side band technique using a benzene capillary as an external standard. In obtaining the spin-coupling constant by measuring the splitting of the CHO doublet the side band frequency was set such that the side band appeared a few counts per second before the doublet. As soon as the side band had been traced, the frequency was changed in such a way as to place the side band a few counts per second after the doublet. By this method a trace of the doublet was obtained carrying a side band marker immediately before and after the doublet. At least 10 such determinations were made in obtaining a given spin-coupling constant. The method was cross-checked by using the standard side band superposition technique. All determinations were *within* ±0.2 c.p.s. of the mean value reported. The chemical shifts of all peaks in both spectra together with the spin-coupling constants (J) are recorded in Table I.

TABLE I

Chemical shifts in c.p.s. from benzene at 40 Mc for ephedrines in 1.5 molar chloroform solution

Compound	C_6H_5	CHO†	CHN*	NCH_3	CCH_3†
(+)-ψ-Ephedrine	−34	+121 +129 (J = 8.2±0.2)	+155	+165	+223 +230
(−)-Ephedrine	−33	+ 68 + 72 (J = 4.0±0.2)	+153	+162	+219 +225

*Central peak of quintuplet.
†Doublet.

DISCUSSION

Spin–Spin Coupling Constant for CH—O/CH—N Interaction

The spin-coupling constant for the interaction of these adjacent protons is twice as great for (+)-ψ-ephedrine (8.2±0.2) as for (−)-ephedrine (4.0±0.2). This observation is of critical importance in establishing the existence of preferred residence in different conformations in the two diastereoisomers. In the first instance the large difference between the constants establishes the fact that a real difference does exist between the time-averaged spin coupling of these two protons. This difference could only arise if preferred residence in different conformations existed. Secondly, the fact that it is the (+)-ψ-ephedrine form which has the higher coupling constant strongly suggests that in this form the preferred relationship between the protons under consideration is trans while in (−)-ephedrine, with the much lower coupling constant, the preferred relationship, if any, is gauche. The order of magnitude of the observed coupling constants and the trans and gauche assignment given above is in keeping with previous observations of Glick and Bothner-By (5) and Lemieux and co-workers (6). The results are also in qualitative agreement with the theoretical calculations of Karplus (4) which predict J values between 8 and 9 c.p.s. for dihedral angles close to 0° or 180° and minimum values of J for angles close to 90°. In terms of the possible conformations shown in Fig. 1, therefore, the J values support a conformation such as (*a*) for the preferred residence form for (+)-ψ-ephedrine but do not support conformer (*y*) as the preferred residence form for (−)-ephedrine. The spectra of the two diastereoisomers, however, contain additional information which is of value in assigning preferred residence conformations.

C—CH_3 Resonance

The chemical shift associated with the C—CH_3 protons is approximately the same in both diastereoisomers. This observation is of importance when compared with the recently observed differences in C—CH_3 shift in the oxazolidone and oxazolidine derivatives of the two ephedrines (7). In these derivatives the ephedrine molecules are bridged across the OH and NH functional groups so that the groups on the adjacent asymmetric centers are constrained to adopt specific spacial relationships to one another. In the (−)-ephedrine form such bridging results in a virtual eclipsing of the phenyl and C—CH_3 groups with a consequent upfield shift of the C—CH_3 resonance due to the diamagnetic anisotropy of the phenyl ring. In the (+)-ψ-ephedrine case bridging in the derivative constrains the phenyl and C—CH_3 groups to adopt a staggered configuration and the upfield shift is not observed. The difference in chemical shift associated with the C—CH_3 protons in the two cases is of the order of 20 c.p.s. The absence of such a difference

in the spectra of the two ephedrines strongly suggests that the C—CH_3 groups in the two diastereoisomers are in the same spacial environment relative to the adjacent phenyl groups. Furthermore, the fact that the C—CH_3 groups in both diastereoisomers are under the same magnetic influence of the adjacent phenyl suggests that the freedom of rotation of the phenyl group and hence its time-averaged anisotropic influence on the methyl is the same in both diastereoisomers. It might be concluded, therefore, that the steric environment of the phenyl in both isomers is the same thus permitting the same freedom of rotation.

Suggested Preferred Residence Conformers

The experimental results discussed above do not appear to be entirely accommodated by any one of the "pure staggered" conformations shown in Fig. 1. This is not altogether surprising since the assumption that the "pure staggered" forms represent the most stable conformations is based solely upon consideration of the effects of non-bonded repulsions or steric effects. In a molecule of the α-β amino alcohol type there are obviously other forces at work in determining the most stable conformations, not the least of which is the energy of hydrogen bonding.

Distribution of Population Between "Off-Staggered" Conformers

In order to accommodate all the n.m.r. spectral evidence presented in this paper, preferred residence conformers of an "off-staggered" form are suggested in Fig. 2. The various experimental facts which are accommodated by the suggested conformers are considered in turn.

(*a*) The spacial relationship of the methyl and phenyl groups are the same in both isomers and the environment of the phenyl group is likewise identical. These facts meet the requirements, noted previously, for similar resonance frequency of the C—CH_3 protons in both isomers.

(*b*) The dihedral angle between the C—H bonds on the two carbon centers in the conformer suggested for (+)-ψ-ephedrine is 150°–160°. According to Karplus (4) this would yield a J_{calc} = 7–8 c.p.s.; this is in good agreement with the observed value of J_{obs} = 8.2 c.p.s. The corresponding dihedral angle for the suggested conformer for (−)-ephedrine (80°–90°) corresponds to a Karplus $J_{calc} \doteqdot 0$ c.p.s. compared with a J_{obs} = 4.0 c.p.s. Two factors may account for this quantitative disagreement. It has

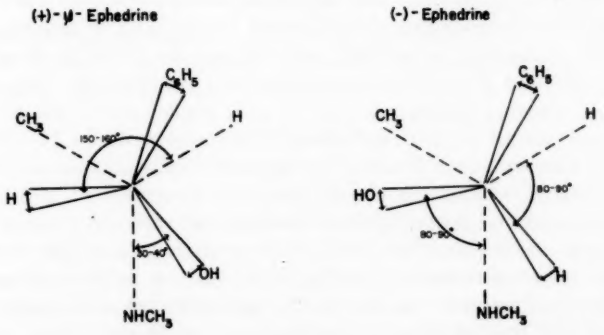

FIG. 2. Suggested preferred residence conformations of the diastereoisomeric ephedrines.

been generally found that the calculated J values tend to be somewhat low, especially in those cases where the coupled protons have a gauche relationship. Lemieux *et al.* (6) reported J values for equatorial proton coupling (dihedral angle approximately 60°) in acetylated sugars between 2 and 4 c.p.s. while the Karplus calculation gives a $J_{calc} = 1.7$ c.p.s. The quantitative disagreement, however, may reflect the fact that other possible conformations are significant in the (−)-ephedrine case since the conformation suggested is not stabilized by intramolecular hydrogen bonding to the same extent as in the ψ-ephedrine case. It should be noted that the dihedral angle in the (−)-ephedrine case cannot be changed without changing the phenyl–methyl relationship. Although a small difference in the C—CH_3 resonance is in fact observed in the two spectra (3–4 c.p.s.), such a difference could easily be due to slight variations in the dihedral angle between phenyl and methyl within the 10° limit of uncertainty shown in the conformers of Fig. 2.

(*c*) For a 30°–40° angle between the C—N and C—O bonds, as suggested in the conformer for (+)-ψ-ephedrine, the N—O center-to-center distance is in the range 2.6–2.7 Å. In the suggested (−)-ephedrine conformer the 80°–90° angle between the amino and hydroxyl groups leads to an N—O distance in the range 3.05–3.15 Å. Pimentel and McClellan (8) report the average O—H- - -N bond distance from 21 examples of such hydrogen bonding to be 2.80 Å with a standard deviation of 0.09 Å. The conformers suggested, therefore, accommodate the experimental evidence presented previously (1) where it was shown that there was a greater tendency to intramolecular hydrogen bonding in the (+)-ψ-ephedrine case; from the bond distances given above it is clear that the N—O distance in the (+)-ψ-ephedrine conformer is within the limiting distance while that for (−)-ephedrine is somewhat greater.

(*d*) It should also be noted that the "off-staggered" conformations suggested in Fig. 2 move the bulky phenyl group further from the bulky methyl and toward the sterically less restrictive hydrogen. In as much as an "off-staggered" conformation is favored this would appear to be a reasonable direction in which to rotate in terms of steric factors.

One outstanding feature of the spectra which has not been considered above is the 55 c.p.s. difference in the chemical shift of the C*H*O protons in the two diastereoisomers. It is admitted that this is a large shift to attribute solely to non-bonding environmental effects and there is no analogous example of this magnitude in the literature. However, it is pointed out that in the (−)-ephedrine case the C*H*O proton is in close proximity to the amino nitrogen lone pair and may experience a downfield shift due to the additional shielding afforded by these electrons. In contrast the same C*H*O proton in the suggested (+)-ψ-ephedrine conformer is partially eclipsed by the C—CH_3 bond on the other center. Bothner-By and Naar-Colin have suggested (9) that the carbon–carbon bond may exert a diamagnetic influence along an axis transverse to the bond axis. If the C*H*O proton experienced such an influence its resonance would be shifted upfield. A combination of these two factors acting in opposite directions on the C*H*O protons in the two isomers might explain the observed shift of 55 c.p.s.

While the observations reported here have been interpreted in terms of unique conformations for the diastereoisomeric pair it is emphasized that these conformations are suggested as the *preferred* residence forms only. In systems such as the ones under study the energy differences between various conformations must, of necessity, be small with the consequence that there will be a distribution of population among the various conformers. The evidence appears convincing, however, that the conformers suggested in Fig. 2 are the most heavily populated in the respective diastereoisomers.

*Distribution of Population Between Pure Staggered Conformers**

While the interpretation offered above accommodates the experimental facts on the basis of a distribution of population amongst "off-staggered" conformers with a preferred residence in the forms shown in Fig. 2, an alternative interpretation is possible based on a population distribution amongst "pure staggered" conformers of the type shown in Fig. 1.

If the gauche proton–proton coupling constant is taken as 2 c.p.s. and the trans value as 12 c.p.s. (these are the more common experimental values and are higher than the calculated Karplus values) then a distribution of (+)-ψ-ephedrine population between the pure staggered forms of Fig. 1 of $a:b:c = 62\%:30\%:8\%$ would yield a value of $J_{calc} = 8.2$ c.p.s. (cf. $J_{obs} = 8.2$ c.p.s.). Similarly for (−)-ephedrine a population distribution of $x:y:z = 40\%:20\%:40\%$ yields $J_{calc} = 4.0$ c.p.s. (cf. $J_{obs} = 4.0$ c.p.s.). Such a population distribution in the diastereoisomeric pair means that there will be 92% of (+)-ψ-ephedrine in conformations having the $NHCH_3$ and OH groups gauche ($a+b$ forms) and favorable for intramolecular hydrogen bonding compared with only 80% in (−)-ephedrine ($x+z$ forms). In addition approximately the same percentages of (+)-ψ-ephedrine ($a+c$ forms = 70%) and (−)-ephedrine ($x+z$ forms = 80%) occupy conformations having the methyl and phenyl groups gauche as required by the observed similarity of the methyl shift in both spectra.

While this explanation of the experimental observations has merit and is probably somewhat less complex than that based on preferred residence in a particular "off-staggered" conformation it also has some dubious features. As pointed out previously, there is no compelling reason to assume that the classical "pure staggered" conformations represent energy minima on the energy versus angle of rotation diagram. In simple symmetrical systems such as ethane, such an assumption is probably correct but the asymmetry of the group interactions in a molecule such as ephedrine does not warrant the assumption that the "pure staggered" conformers represent energy minima. It is also doubtful whether the difference between 80% and 92% population in conformers favorable for intramolecular hydrogen bonding is sufficiently large to account for the considerable difference observed in the intramolecular hydrogen-bonding ability of the two diastereoisomers. This is even more questionable when the difference between 70% and 80% population in the conformers with methyl and phenyl gauche to one another is considered to be sufficiently small to have little effect on the position of the $C—CH_3$ resonance.

Although there is insufficient experimental evidence to distinguish conclusively between the two possible explanations, that based on preferred residence in an "off-staggered" conformation appears to be the more plausible.

CONCLUSION

The problem of determining which conformations represent those in which a molecule resides preferentially in systems where the various possible conformers are separated by low-energy barriers requires the application of the most refined techniques. In this paper it has been shown that in the case of the ephedrines, where the energy barriers between the various conformers are the result of hydrogen-bonding phenomena and no-bond type interactions between adjacent groups on two carbon atoms joined by a single bond, the techniques of n.m.r. spectroscopy may provide the necessary refinement. By utilizing the n.m.r. technique of studying intra- and inter-molecular hydrogen

**The author is indebted to the referee for bringing this alternative interpretation to his notice.*

bonding by dilution, the anisotropic properties of the phenyl group and spin–spin coupling phenomena, assignment of those conformers representing preferred residence forms appears possible.

The further application of this technique seems obvious in such systems as substituted diols, diamines, hydroxy ketones, and similar molecules in which some or all of the necessary phenomena can be observed.

ACKNOWLEDGMENT

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SANDARAC ACIDS: 6β-HYDROXYSANDARACOPIMARIC ACID[1]

J. W. ApSimon[2] and O. E. Edwards

ABSTRACT

The resin from *Callitris quadrivalvis* Vent. Decad. (Sandarac resin) has been shown to contain 6β-hydroxysandaracopimaric acid (6β-hydroxy-7-epipimara-9(14),19-dienoic acid).

Recently we reported the isolation of what appeared to be an hydroxypimaric acid from commercial Sandarac resin (1) derived from the North African tree *Callitris quadrivalvis* Vent. Decad. We now present proof that this is the 6β-hydroxy derivative of sandaracopimaric acid, the structure and stereochemistry of which has been established (1, 2, 3).

The acid, m.p. 269–270°, analyzed correctly for $C_{20}H_{30}O_3$. Characteristic bands for a vinyl group at 904 and 987 cm^{-1} were present in its infrared spectrum. These were absent in the dihydro acid produced by rapid uptake of 1 mole of hydrogen over palladium. The dihydro acid had absorption at 823 cm^{-1}, suggestive of the presence of a trisubstituted double bond. The presence of this feature was confirmed by one-hydrogen signals near $\tau = 5$ (CCl_4) in the N.M.R. spectrum of a number of derivatives of the acid.

The infrared spectrum of the original acid and the dihydro acid had peaks near 3400 cm^{-1} which were absent in their readily prepared monoacetates. Thus all the functions of a hydroxypimaric acid had been identified. The hydroxyl group was shown to be secondary by oxidation of the dihydro acid to a keto acid. The structure and stereochemistry of the skeleton was then established by Wolff–Kishner reduction of the keto acid. The product was identical in all respects with dihydrosandaracopimaric acid (I) (1).

The N.M.R. spectrum (CCl_4) of the methyl ester of the keto dihydro acid had a one-hydrogen signal at $\tau = 4.76$ (vinyl hydrogen) and what appeared to be a fairly sharp two-hydrogen signal (half band width 5 c.p.s.) at $\tau = 7.66$ superimposed on a broad unresolved signal. This had to be associated with a methylene adjacent to the ketone carbonyl. The only locations for the carbonyl which seemed compatible with the apparent lack of coupling of this methylene group with other hydrogens were C-5 and C-10. However, the low field signal was absent for the 13-hydrogen expected if the carbonyl was on C-5, and the methylene signal was at too high field for one flanked by a 10-carbonyl and the double bond (expected around $\tau = 7$). In addition, neither base nor acid treatment of the keto acid moved the double bond into conjugation with the carbonyl. Hence neither of these positions for the oxygen appeared likely.

In order to establish the oxygen location the dihydro keto acid was treated with methyl magnesium iodide. The resulting hydroxy acid was dehydrogenated using selenium. The major product was 1,6,7-trimethylphenanthrene (II), thus proving that the keto acid was 6-keto-19,20-dihydrosandaracopimaric acid (III).

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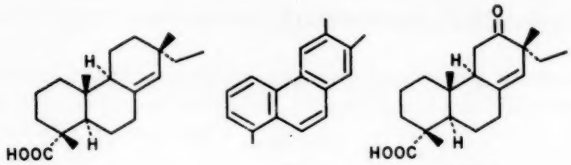


I II III

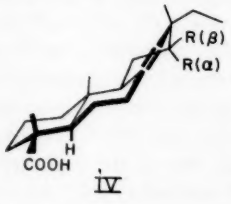
In retrospect, an important clue about the location of the oxygen could have been the chemical shift on the 18-methyl signal in the 6-ketone, as compared with that in the other derivatives (Table I). A comparable shift for the C-18 in 17a-keto-D-homosteroids has been recorded (4).

TABLE I

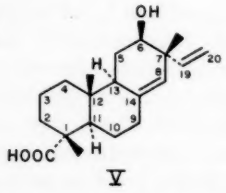
Chemical shifts in τ in carbon tetrachloride ($Si(CH_3)_4$ as internal standard)

	C_{16}	C_{18}	C_{17}	Vinyl proton	COOH	$COOCH_3$
Methyl dihydrosandaracopimarate	8.89	9.18	9.26	5.02	—	6.48
Methyl dihydro-6-hydroxysandaracopimarate	8.87	9.16	9.21	5.11	—	6.53
Methyl dihydro-6-ketosandaracopimarate	8.89	9.00	9.27	4.76	—	6.38
Dihydro 6-acetoxysandaracopimaric acid	8.88	9.11	9.22	5.18	−1.14	—

There remained the problem of assigning configuration to the hydroxyl group of the original acid. Since the epimeric hydroxyls on C-6 should be true axial and true equatorial in the half-chair conformation of ring C (see IV) we chose to examine the products of borohydride and sodium in alcohol reduction of the 6-ketone. In both cases, high yields of product with the original hydroxyl configuration were formed. This established the hydroxyl conformation as equatorial. Thus the hydroxyl in the original acid is β oriented (see IV) and the new acid is 6β-hydroxysandaracopimaric acid (V) (6β-hydroxy-7-epipimara-8(14),19-dienoic acid).



IV

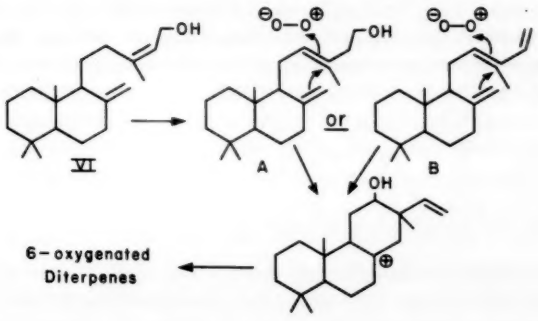


V

This acid takes its place with podocarpic acid, ferruginol, Δ^9-dehydroferruginol, xanthoperol, sugiol (5), nimbiol (6), royleanone (7), hinokiol and hinokione (8), vinhaticoic acid (9), and possibly the tanshinones (10) as a 6-oxygenated diterpene. The occurrence of numerous 6-oxygenated diterpenes leads us to suggest that the cyclization to form ring C of the tricyclic diterpenes can take place not only from VI or manool (11) but also in some plants from the double bond isomer A or triene B.[3] Proton-initiated cyclization of these would lead to hydroxyl-free molecules, but cyclization initiated by oxygen[4] would lead to the 6-oxygenated diterpenes listed above.

[3]*This triene B has recently been isolated from Dacrydium biforme and named biformene (12).*

[4]*The work of Tchen and Bloch (13) established the initiation of squalene cyclization in yeast to give 3-hydroxy steroids to be by atmospheric oxygen, presumably enzyme activated.*



EXPERIMENTAL

Rotations were of ethanol solutions, infrared spectra were of nujol mulls, and melting points were taken on a Kofler hot stage.

6-Hydroxysandaracopimaric Acid

The acid was obtained as described previously (1). It crystallized from acetone as colorless needles, m.p. 269–270°, $[\alpha]_D$ −11° (*c*, 0.4). Its infrared spectrum had weak bands at 904 and 987 cm^{-1} (vinyl group) and 822 cm^{-1} ($>C=C<^{H}$), and a strong band at 3360 cm^{-1} (hydroxyl) and at 1695 cm^{-1} (—COOH).

6-Hydroxy-19,20-dihydrosandaracopimaric Acid

6-Hydroxysandaracopimaric acid (480 mg) in ethanol (250 ml) was reduced with hydrogen in the presence of presaturated 10% palladium on charcoal (400 mg). In 3 minutes, 36 ml of hydrogen were absorbed (calc. for 1 mole 35 ml). The product crystallized from methanol or ethanol as colorless plates (450 mg), m.p. 294–295°, $[\alpha]_D$ +17.5 (*c*, 0.28). Found: C, 75.12; H, 9.98. Calc. for $C_{20}H_{32}O_3$: C, 74.96; H, 10.06%. Infrared spectrum: ν_{max} 3360 cm^{-1} (hydroxyl); 1695 cm^{-1} (—COOH); 823 cm^{-1} ($>C=C<^{H}$).

6-Acetoxysandaracopimaric Acid

6-Hydroxysandaracopimaric acid (200 mg), pyridine (2 ml), and acetic anhydride (2 ml) were allowed to stand overnight at room temperature. The colorless solution was poured into water and the solid product crystallized from *n*-hexane. Recrystallization from the same solvent gave colorless prisms (200 mg), m.p. 170°, $[\alpha]_D$ −51° (*c*, 1.56). Found: C, 73.41; H, 8.79. Calc. for $C_{22}H_{32}O_4$: C, 73.30; H, 8.95. Infrared spectrum: ν_{max} 1730 cm^{-1} (acetate); 1700 cm^{-1} (—COOH); 909 cm^{-1} and 992 cm^{-1} (vinyl group); and 826 cm^{-1} ($>C=C<^{H}$).

6-Acetoxy-19,20-dihydrosandaracopimaric Acid

Treatment of the dihydro acid (100 mg) in the manner described above yielded colorless prisms (90 mg), m.p. 183°, from *n*-hexane. $[\alpha]_D$ −27.5° (*c*, 0.08). Found: C, 73.09; H, 9.21. Calc. for $C_{22}H_{34}O_4$: C, 72.89; H, 9.45. Infrared spectrum: ν_{max} 1725 cm^{-1}, 1700 cm^{-1} (—COOH).

Methyl 6-Hydroxysandaracopimarate

6-Hydroxysandaracopimaric acid (50 mg) in methanol (25 ml) was treated with excess ethereal diazomethane during 15 minutes. Excess diazomethane was destroyed with acetic acid. The solution was washed well with sodium bicarbonate and water; drying and evaporation yielded a crystalline residue (50 mg). Recrystallization from *n*-hexane gave colorless needles (45 mg), m.p. 94°. The analytical sample was sublimed at 80°/10^{-3} mm. Found: C, 76.02; H, 9.61; OMe, 9.12. Calc. for $C_{20}H_{29}O_2(OMe)$: C, 75.86; H, 9.70; OMe, 9.34. Infrared spectrum: ν_{max} 3300 cm^{-1} (hydroxyl), 1730 cm^{-1} (—COOMe), 909 and 992 cm^{-1} (vinyl group), and 827 cm^{-1} ( ).

Methyl 6-Hydroxy-19,20-dihydrosandaracopimarate

The dihydro acid (30 mg) on treatment with diazomethane in the manner described above yielded colorless needles (27 mg), m.p. 112°, from *n*-hexane. Found: C, 75.20; H, 10.06; OMe, 9.04. Calc. for $C_{20}H_{31}O_2(OMe)$: C, 75.40; H, 10.25; OMe, 9.25. Infrared spectrum: ν_{max} 3360 cm^{-1} (hydroxyl), 1730 cm^{-1} (—COOMe), and 828 cm^{-1} ( ).

6-Keto-19,20-dihydrosandaracopimaric Acid

6-Hydroxy-19,20-dihydrosandaracopimaric acid (570 mg) in benzene (50 ml) and acetic acid (50 ml) was treated with sodium dichromate dihydrate (200 mg) in acetic acid (10 ml) at room temperature. Next day the green reaction mixture was poured into water and the benzene layer separated. The aqueous layer was further extracted with benzene (4×25 ml). The combined benzene extracts were dried and evaporated, yielding a crystalline residue (470 mg). Recrystallization from ether/*n*-hexane in an acetone – dry ice bath gave colorless prisms, m.p. 149°. The analytical sample was sublimed at 120°/10^{-3} mm. $[\alpha]_D$ −79° (*c*, 0.38). Found: C, 75.43; H, 9.61. Calc. for $C_{20}H_{30}O_3$: C, 75.43; H, 9.50. Infrared spectrum: ν_{max} 1705 cm^{-1} ( ), 1690 cm^{-1} (—COOH).

Methyl 6-Keto-19,20-dihydrosandaracopimarate

The above keto acid (110 mg) in ether (10 ml) and methanol (5 ml) was treated with excess ethereal diazomethane during 15 minutes. Excess diazomethane was decomposed with acetic acid and the ethereal solution washed with sodium bicarbonate and water. The dried solution on evaporation yielded a colorless crystalline product (112 mg), m.p. 88–89°. On recrystallization from pentane and sublimation, this gave prisms, m.p. 89°. $[\alpha]_D$ −71° (*c*, 1.4). Found: C, 75.77; H, 9.53; OMe, 9.22. Calc. for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70; OMe, 9.34. Infrared spectrum: ν_{max} 1714 cm^{-1} (—COOMe), 1706 cm^{-1} (6-membered ketone).

Wolff–Kishner Reduction of 6-Keto-19,20-dihydrosandaracopimaric Acid

6-Keto-19,20-dihydrosandaracopimaric acid (58 mg) in hydrazine hydrate (2 ml) and triethylene glycol (2 ml) was heated to 140° during 45 minutes. Potassium hydroxide (1 g) was added during 5 minutes and the temperature gradually raised to 200° for 5 hours. The reaction mixture was cooled, acidified with 2 *N* H_2SO_4, and ether extracted. The ether extract was washed well with water, dried, and evaporated, yielding a colorless crystalline solid (43 mg), m.p. 175–179°. Recrystallization from aqueous methanol gave needles, m.p. 177–179° undepressed on mixture with dihydro sandaracopimaric acid, and having the requisite infrared spectrum, $[\alpha]_D$ +25° (*c*, 1.25). Found: C, 78.76; H, 10.62. Calc. for $C_{20}H_{32}O_2$: C, 78.94; H, 10.52.

Reaction of Methyl Magnesium Iodide with 6-Ketodihydrosandaracopimaric Acid

The keto acid (1.54 g) in dry ether (20 ml) was added gradually to methyl magnesium iodide at 0°, prepared from magnesium (0.75 g) and methyl iodide (5 ml) in ether (20 ml). A colorless solid was precipitated. The mixture was vigorously stirred overnight at room temperature. It was poured onto a mixture of ice (20 mg) and 2 *N* H_2SO_4 (50 ml), then extracted with ether. The ether extract was washed well with sodium bisulphite and water. Drying and evaporation gave a colorless semicrystalline product (1.3 g). Crystallization from chloroform/*n*-hexane yielded small colorless prisms (750 mg), m.p. 218°, $[\alpha]_D$ +63° (*c*, 0.4). Found: C, 75.30; H, 10.06. Calc. for $C_{21}H_{34}O_3$: C, 75.40; H, 10.25. Infrared spectrum ν_{max} at 3500 cm^{-1} (OH), 1700 cm^{-1} (—COOH).

Selenium Dehydrogenation of 6-Hydroxy-6-methyl-19,20-dihydrosandaracopimaric Acid

The Grignard product (600 mg) and selenium (2 g) were intimately mixed and heated at 300° C for 17 hours. Hydrogen selenide production was followed on a tower of bleaching powder. The mixture was cooled and the black solid was extracted several times with boiling benzene. The benzene extract was refluxed with freshly precipitated silver for 1 hour, filtered, and refluxed again with fresh silver. Drying and evaporation yielded yellow prisms (350 mg), m.p. 105–120°. Chromatography on Grade IV alumina in pentane gave colorless prisms (290 mg), m.p. 110–117°. Recrystallization from aqueous ethanol gave colorless needles, m.p. 122–123°. Sublimation at $120/10^{-3}$ mm gave colorless prisms, m.p. 123°. Found: C, 92.52; H, 7.20. Calc. for $C_{17}H_{16}$: C, 92.68; H, 7.32. Its ultraviolet spectrum was identical in all respects with that reported for 1,6,7-trimethyl phenanthrene (14). Its picrate separated as orange needles from ethanol, m.p. 167–168° (reported m.p.167° (15)). Found: C, 61.34; H, 4.39. Calc. for $C_{23}H_{19}O_7N_3$: C, 61.47; H, 4.26. Its styphnate crystallized from acetic acid as orange needles. Sublimation gave the analytical sample, m.p. 171° (reported 111°, error?). Found: C, 59.22; H, 3.91. Calc. for $C_{23}H_{19}O_8N_3$: C, 59.35; H, 4.12.

The phenanthrene (91.5 mg) in acetic acid (5 ml) was oxidized with chromic trioxide (100 mg, 2.2 mole) in acetic acid (5 ml) on a steam bath for 2 hours. The reaction mixture was diluted and extracted with ether. The ether solution was washed with potassium carbonate solution and water. It was then dried and evaporated, yielding an orange crystalline product (80 mg), m.p. 215–220°. Sublimation gave orange prisms of 1,6,7-trimethyl phenanthraquinone, m.p. 223° (reported m.p. 222° (15)). The quinoxaline of the phenanthraquinone formed buff needles from aqueous ethanol, m.p. 188–189° (reported m.p. 189–190° (15)).

Reduction of the Keto Acid

6-Keto-19,20-dihydrosandaracopimaric acid (200 mg) in 80% methanol (30 ml) was treated with sodium borohydride (150 mg) and allowed to stand at room temperature for 1 hour. The mixture was acidified with 2 *N* hydrochloric acid, methanol removed *in vacuo*, and ether extracted. The ether extract was dried and evaporated, yielding a yellow oil (200 mg) which was dissolved in methanol, refluxed with charcoal, filtered, and concentrated (5 ml). On cooling, colorless needles formed (105 mg), m.p. 294–295°, $[\alpha]_D$ +17° (*c*, 0.24). Its infrared spectrum was identical with that of dihydro-6-hydroxy sandaracopimaric acid and a mixed melting point was undepressed. Sodium in alcohol reduction of the keto acid (100 mg) afforded the same product (72 mg), m.p. and mixed m.p. 295°, $[\alpha]_D$ +19° (*c*, 0.34), and having the requisite infrared spectrum.

Attempted Isomerization of the Keto Acid

Hydrogen chloride was passed into a solution of 6-keto-19,20-dihydrosandaracopimaric

acid (30 mg) in dry chloroform (10 ml) at −5° for 4 hours. The chloroform solution was washed free from mineral acid with water, and then dried and evaporated to give a colorless crystalline product (28 mg), m.p. and mixed with starting material 149° and having the requisite infrared spectrum. The keto acid was unchanged by warm 5% sodium hydroxide or by traces of perchloric acid. Similar results were observed with the dihydro hydroxy acid and the dihydro acetoxy acid.

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THE Hg $6(^3P_1)$-PHOTOSENSITIZED DECOMPOSITION OF NITRIC OXIDE[1]

OTTO P. STRAUSZ AND HARRY E. GUNNING

ABSTRACT

The reaction of NO with Hg $6(^3P_1)$ atoms has been studied under static conditions at 30°, over the pressure range 1–286 mm. The products were found to be N_2, N_2O, and higher oxides of nitrogen. At NO pressures exceeding 4 mm, the total rate of formation of N_2+N_2O was constant, while the ratio N_2O/N_2 increased linearly with the substrate pressure. The rate was found to vary directly with the first power of the intensity at 2537 Å, and a value of 1.9×10^{-3} moles/einstein was established for the quantum yield of N_2+N_2O production. In the proposed mechanism, reaction is attributed to the decomposition of an energy-rich dimer, $(NO)_2^*$, which is formed by the collision of electronically excited ($^4\Pi$) NO molecules with those in the ground state. The $(NO)_2^*$ species is assumed to decompose by the steps: $(NO)_2^* \rightarrow N_2 + O_2$ and $(NO)_2^* + NO \rightarrow N_2O + NO_2$. The mechanism satisfactorily explains the observed behavior of the system.

INTRODUCTION

Although there have been several studies of the photolysis of NO, the nature of the primary process is still in doubt. Thus MacDonald (1) studied the reaction in the 70–630 mm region, using 1860–1990 Å radiation; he concluded that 1/10th of the reaction led to N_2O formation, and that the remainder yielded N_2. He postulated reaction to proceed through the interaction of excited NO molecules with those in the ground state. Flory and Johnston (2) found, in the low pressure region, 0.02–7 mm, no evidence of N_2O formation; they interpreted the primary process as predissociation. At low pressures they found the active line to be 1832 Å. They concluded that any decomposition by absorption at 1849 Å could only occur at higher pressures. Recently Gaydon (3) has reported that no trace of photodecomposition could be detected when NO, at atmospheric pressure, was exposed to radiation from an iron arc. This polychromatic source gives no emission below 2084 Å.

The reaction of NO with Hg $6(^3P_1)$ atoms was first studied by Noyes (4). He established that the rate was (*a*) first order in light intensity and (*b*) first order in substrate pressure in the range 0.003–0.13 mm. The pressure dependence approached zero order at higher pressures. On a pressure-change basis, it was deduced that N_2 was the only gaseous product. From the kinetic behavior and the energetics of the reaction, Noyes concluded that the rate-determining step was the formation of long-lived vibrationally excited NO molecules.

McGilvery and Winkler (5) found no reaction of NO with Hg $6(^3P_1)$ atoms; however, they observed a fast reaction with Hg $6(^1P_1)$ atoms. Only N_2 and higher oxides were detected as products. The addition of N_2 was found to decrease the rate. Reaction was attributed to N—O bond scission by the Hg $6(^1P_1)$ atoms. Recently Bernstein and Hoffman (6) have reinvestigated the reaction with Hg $6(^3P_1)$ atoms. They measured the rate of N_2 formation, and also the $^{14}N/^{15}N$ isotope effect. In their mechanism they followed the suggestion of Fallon, Vanderslice, and Mason (7) that the quenching collision formed long-lived NO($^4\Pi$) molecules, for which the lowest vibrational level was estimated to lie 4.64 ± 0.10 ev above the lowest vibrational level of the ground state. For this state, radiative reversion to the ground state was considered of low probability. The proposed mechanism (6) included the steps:

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Contribution from the Department of Chemistry, University of Alberta, Edmonton, Alberta.

$$Hg^* + NO \rightarrow NO^* + Hg; \quad (a)$$

$$Hg^* + NO \rightarrow NO_V + Hg'; \quad (b)$$

$$Hg^* \rightarrow Hg + h\nu; \quad (c)$$

$$Hg^* + NO^* \rightarrow N + O + Hg; \quad (d)$$

$$N + NO \rightarrow N_2 + O; \quad (e)$$

$$O + NO \rightarrow NO_2 \text{ etc.}; \quad (f)$$

where $Hg^* = Hg\ 6(^3P_1)$; $Hg' = Hg\ 6(^3P_0)$; $NO^* = NO(^4\Pi)$, and NO_V = vibrationally excited NO. An equivalent mechanism was suggested by Cvetanović (8). Here, for (*b*) and (*d*) above, were substituted (*b'*) $NO^* + NO \rightarrow 2NO$ and (*d'*) $NO^* + NO \rightarrow N + NO_2$.

Finally Cojan and Taboue (9) have reported some interesting experiments in which NO at 0.1 mm was exposed to radiation from a cooled Hg arc, in the presence of mercury vapor. By absorbiometric analysis, with the magnetic filter technique, they showed that the mercury strongly bonded to the wall of the reaction cell was enriched in ^{202}Hg. These results will be discussed later in this paper.

The present study was prompted by a recent investigation in this laboratory (10) of the reaction of CO_2 with Hg $6(^3P_1)$ atoms. Here it was shown that decomposition proceeds through a process, second order in the light intensity, involving collision of two excited species. It seemed of interest to determine whether a similar type of process was operative in the NO reaction. The details of the investigation follow.

EXPERIMENTAL

The apparatus and general experimental technique have been previously described (10). The nitric oxide (Matheson) was subjected to several low-temperature distillations before use. Analysis by G.L.P.C. showed that the only impurity was N_2O at a concentration of less than 0.01%. After each run, the products were removed from the unreacted substrate and analyzed by G.L.P.C.

RESULTS

The products of the reaction were N_2 and N_2O, together with higher oxides of nitrogen; the latter were observed to attack the mercury in the reaction cell. Analysis of the cell deposit showed the presence of NO_2^- ion.

The measured rates of N_2 and N_2O formation, in μmoles/hour, are presented, for runs of 60 minutes in duration, in Table I. The absorbed light intensity at 2537 Å(I_a), determined with propane as actinometer (11, 12), was 3.34×10^{-5} einstein/minute. The maximum rate of N_2 formation occurred at a NO pressure of 3.25 mm, where 4.0 μmoles were formed per hour.

In Table II, the total rate, $R(N_2+N_2O)$, is shown as a function of $P(NO)$, for 10-mm pressure intervals up to $P(NO) = 120$ mm. From Table II it is apparent that $R(N_2+N_2O)$ is constant within the experimental error at 3.82 μmoles/hour. For the quantum yield, $\Phi(N_2+N_2O)$, we obtain 1.9×10^{-3} moles/einstein. It should be noted that the run at $P(NO) = 286$ mm was made with $I_a = 7.61\times10^{-5}$ einstein/minute. At this light intensity, $R(N_2)$ and $R(N_2O)$ were respectively 3.79 and 4.60 μmoles/hour. Thus $\Phi(N_2+N_2O)$ was 1.8×10^{-3}, in satisfactory agreement with the data at the lower light intensity. Hence, while $\Phi(N_2)$ decreases with increasing $P(NO)$, and $\Phi(N_2O)$ increases, the sum $\Phi(N_2+N_2O)$ is independent of the substrate pressure, in the complete quenching region.

TABLE I

The rates of N_2 and N_2O formation as a function of the NO pressure

P(NO) (mm)	$R(N_2)$ (μmoles/hour)	$R(N_2O)$ (μmoles/hour)
1.01	3.44	
3.25	4.00	
5.06	3.93	
10.3	3.86	
12.3	3.76	
18.0		0.26
21.5		0.35
21.6		0.31
22.3	3.53	0.41
33.2		0.40
40.0	3.20	0.49
58.0	3.09	0.82
69.6	3.08	0.83
79.5	2.79	
120	2.76	1.27
286	1.64	2.11

TABLE II

The total mean rate of N_2+N_2O formation as a function of NO pressure

P(NO) (mm)	$R(N_2+N_2O)$ (μmoles/hour)	P(NO) (mm)	$R(N_2+N_2O)$ (μmoles/hour)
10	4.05	70	3.73
20	3.94	80	3.73
30	3.87	90	3.74
40	3.80	100	3.79
50	3.77	110	3.81
60	3.75	120	3.86

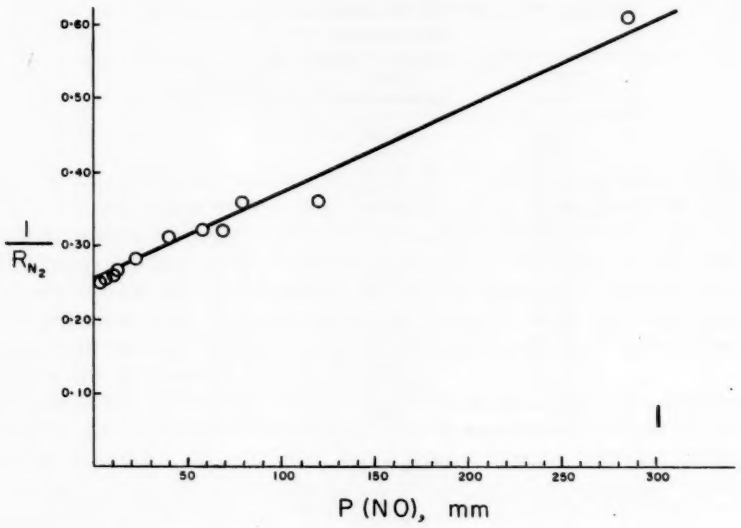
Mean value = 3.82 μmoles/hour

In Fig. 1, the reciprocal rate, $1/R(N_2)$, is shown to vary linearly with P(NO). Similarly, it can be seen from Fig. 2 that the quantity $(NO)/R(N_2O)$ is a linear function of P(NO).

To determine the dependence of the rate upon the light intensity, a doughnut-type Vycor filter was fitted axially over the reaction cell, within the coils of the resonance lamp. The filter, 110 mm in length, 35 mm I.D., and 60 mm O.D., was filled with bromine vapor at a pressure of 170 mm. Its transmission was 55.7% at 2537 Å, and less than 1% at 4047 Å. With the filter, $R(N_2+N_2O)$ was 54% of the value without the filter, confirming Noyes' observation (4) that the rate is proportional to I_a. Since the rate is insensitive to the 100-fold reduction in intensity at 4047 Å, there seems little basis for the stepwise excitation mechanism proposed by McGilvery and Winkler (5).

In Fig. 3, $\Phi(N_2O)/\Phi(N_2)$ is shown as a function of P(NO). The relation is a linear one, within the experimental error.

In order to examine the possibility that the N_2 product might arise in secondary quenching by N_2O, a few runs were performed with added N_2O. In Fig. 4, the rate of N_2O disappearance is plotted against the percentage of added N_2O, for P(NO) constant at 29.4 mm. From the data it is estimated that the rate of decomposition of added N_2O is less than 1/10th of $R(N_2)$ for pure substrate. It is concluded that N_2 is indeed a primary product of the reaction of NO with Hg $6(^3P_1)$ atoms.



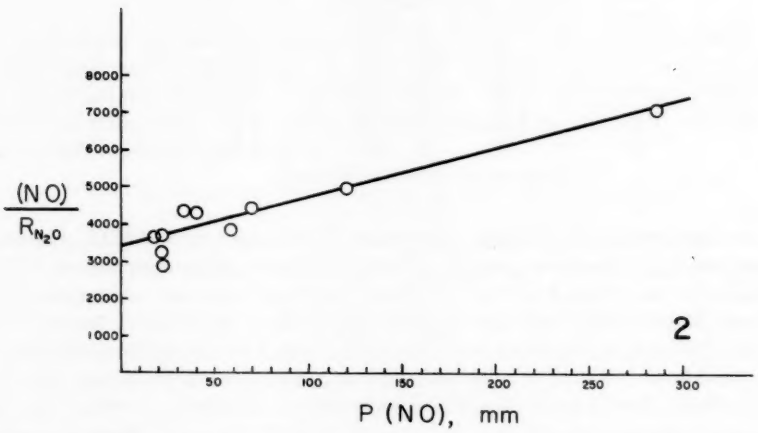
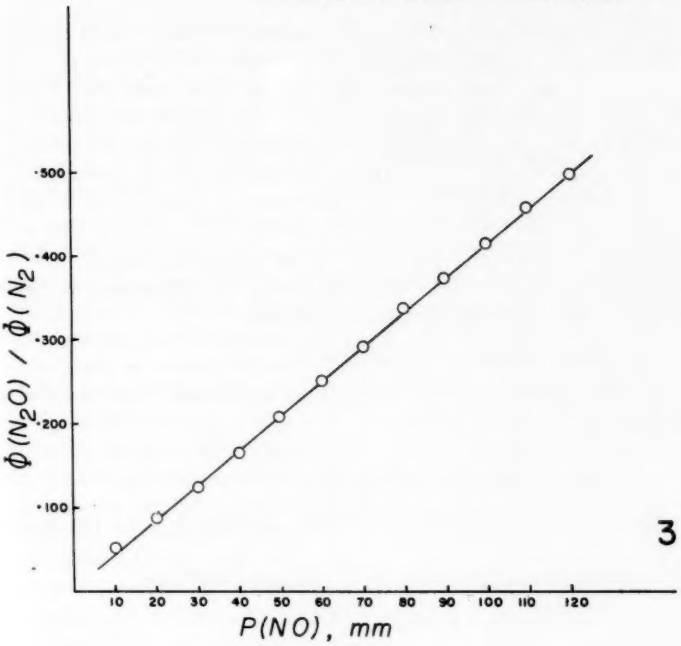


FIG. 1. The reciprocal of the rate of N_2 formation, in (μmoles/hour)$^{-1}$, as a function of the NO pressure, for I_a = 33.4 μeinstein/minute.
FIG. 2. (NO)/R_{N_2O} in hours, as a function of the NO pressure, for I_a = 33.4 μeinstein/minute.

DISCUSSION

The results of the present study lend strong support to the original suggestion of Noyes (4) that the reaction involves primary formation of excited NO molecules. Thus, the presence of N_2O as a major reaction product, a fact not previously reported, could only be explained by interactions of NO molecules in which at least one of the collisional partners is energized. It is also pertinent to note that N atoms react with NO to form N_2, but not N_2O (13).

In order to explain the kinetic behavior of the reaction, as revealed in the present study, the following mechanism is proposed:



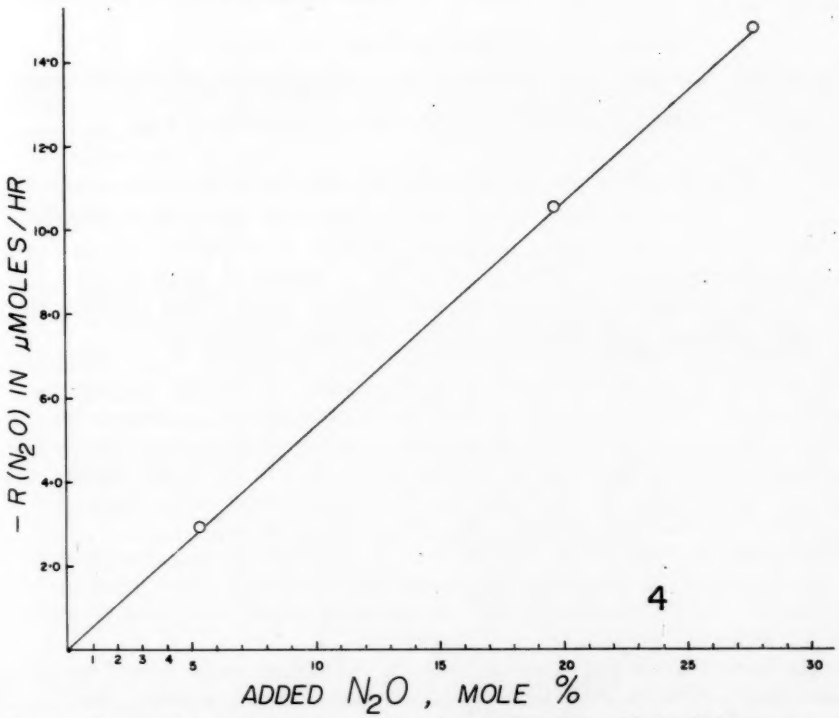


FIG. 3. The variation in the quantum yield ratio, $\Phi(N_2O)/\Phi(N_2)$, with the NO pressure.
FIG. 4. The rate of disappearance of N_2O, in μmoles/hour, as a function of the mole% of added N_2O, for a constant NO pressure of 29.4 mm.

$$Hg + h\nu \rightarrow Hg^* \qquad [I_a]$$

$$Hg^* \rightarrow Hg + h\nu \qquad [1]$$

$$Hg^* + NO \rightarrow NO^* + Hg \qquad [2]$$

$$NO^* + NO \rightarrow 2NO \qquad [3]$$

$$NO^* + NO \rightarrow (NO)_2^* \qquad [4]$$

$$(NO)_2^* \rightarrow N_2 + \text{oxygen} \qquad [5]$$

$$(NO)_2^* + NO \rightarrow N_2O + NO_2 \qquad [6]$$

where $Hg^* = Hg\ 6(^3P_1)$, $NO^* = NO\ (^4\Pi)$, and $(NO)_2^*$ is an energy-rich dimer.

In the complete quenching region, i.e. for $P(NO)$ above ca. 4 millimeters, the rate of (N_2+N_2O) formation from the above mechanism would be

$$R(N_2+N_2O) = I_a k_4/(k_3+k_4).$$

Thus the combined rate would be directly proportional to I_a, and independent of $P(NO)$, in agreement with our findings (Table II).

For the quantum yield ratio, we obtain

$$\Phi(N_2O)/\Phi(N_2) = k_6(NO)/k_5,$$

which requires that the ratio be a linear function of $P(NO)$, passing through the origin, as seen in Fig. 3.

Furthermore, from the mechanism, the rate of N_2 formation would be

$$R(N_2) = I_a k_4 k_5/(k_3+k_4)[k_5+k_6(NO)],$$

and the rate of N_2O formation

$$R(N_2O) = I_a k_4 k_6(NO)/(k_3+k_4)[k_5+k_6(NO)].$$

By rearranging the above rate expressions, the following linear relations are obtained:

$$1/R(N_2) = (k_3+k_4)/(I_a k_4)+(k_3+k_4)(k_6)(NO)/(I_a k_4 k_5)$$

and

$$(NO)/R(N_2O) = (k_3+k_4)(k_5)/(I_a k_4 k_6)+(k_3+k_4)(NO)/(I_a k_4).$$

From Figs. 1 and 2 respectively, it can be seen that the expressions $1/R(N_2)$ and $(NO)/R(N_2O)$ are indeed linear functions of $P(NO)$. Furthermore the mechanism requires that the intercept at $P(NO) = 0$, in Fig. 1, should be equal to the slope in Fig. 2. For the intercept in Fig. 1 we obtain 0.26 hour μmole^{-1}, and for the slope in Fig. 2, 0.24 hour μmole^{-1}, in agreement with the proposed mechanism.

In the proposed mechanism, we have adopted the suggestion of Fallon, Vanderslice, and Mason (7) that reaction [2] leads to the formation of NO ($^4\Pi$). Support for our postulation of the $(NO)_2^*$ species comes from the work of Spindel and Stern (14), who found that a rapid exchange occurs among isotopic nitric oxides at room temperature. At a total pressure of 20 mm, complete exchange occurred in ca. 15–30 seconds. Even at a pressure of 60–100 μ, the exchange was still detectable. It seems likely that the exchange takes place through a square-type dimer intermediate.

The low quantum yield of the reaction, on the basis of the proposed mechanism, would require that [4] be extremely inefficient compared with [3]. Now, from our data, $\Phi(N_2+N_2O) = 1.9\times10^{-3}$, and from the mechanism this quantity would be equal to $k_4/(k_3+k_4)$. Hence k_4/k_3 would be ca. 1.9×10^{-3}.

From the linear slope in Fig. 3, we obtain $k_6/k_5 = 77.5$ liter/mole. Now if we assume a collision cross section of 20 Å^2 for [6], and reaction at every collision, then $k_5 = 2$

$\times 10^{11}/77.5 = 2.6\times 10^{9}$/second. This leads to an estimate for the lifetime, τ, of $(NO)_2^*$ of $1/k_5 = 3.8\times 10^{-10}$ second. The value should be regarded as minimal, since a steric factor less than unity in k_6 would increase τ.

Finally we would like to comment on the isotope effect observed by Cojan and Taboue (9), in the irradiation of a mixture of Hg vapor and 0.1 mm of NO. In unpublished work in this laboratory (15), it has been found that the behavior observed by Cojan and Taboue is characteristic of substrates which convert Hg $6(^3P_1)$ atoms to the $6(^3P_0)$ state. Thus when Hg vapor was admixed with substrates such as N_2, H_2O, and NH_3, and exposed to the radiation from a ^{202}Hg electrodeless discharge, it was observed that the mercury in the cell rapidly became transparent to the ^{202}Hg-hyperfine component at 2537 Å. Apparently the metastable ^{202}Hg atoms had diffused to the wall and become chemisorbed on the surface. The evidence for this is that the normal adsorption could be re-established by heating the cell to drive off the mercury from the wall. Furthermore with addends such as H_2, which quench the $6(^3P_1)$ atoms directly to the $6(^1S_0)$ state, no such change in absorption with time was observed. It is our opinion that the isotope effect found by Cojan and Taboue (9) arises for the following reasons. In the cell the concentration of ^{202}Hg $6(^3P_1)$ atoms will be higher than the natural isotopic abundance for this isotope, owing to its large absorption coefficient (9). By collision with NO, metastable atoms are formed, which will be enriched in ^{202}Hg. These atoms can diffuse to the wall and form a complex with adsorbed NO. It would appear that Hg $6(^3P_0)$ atoms do not possess sufficient energy to convert NO to the $^4\Pi$ state, by reaction [2]. If these conclusions are correct, it would follow that the $^4\Pi$ state must lie between 4.67 and 4.88 ev above the ground state.

CONCLUSIONS

As a result of the present study, it can be concluded that both N_2O and N_2 are major primary products of the reaction of NO with Hg $6(^3P_1)$ atoms at 30°. Reaction must proceed via the initial formation of excited NO, likely in the $^4\Pi$ state, which appears to be inefficiently converted by collision with the substrate to an excited dimer. From this intermediate, N_2 is formed by unimolecular decomposition, while N_2O arises through interaction of the dimer with the substrate.

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HALOGEN ATOM REACTIONS

I. THE ELECTRICAL DISCHARGE AS A SOURCE OF HALOGEN ATOMS[1]

E. A. OGRYZLO

ABSTRACT

A number of surface poisons have been found to prevent the rapid recombination of chlorine, bromine, and iodine atoms. Hence these atoms can now be obtained in large concentrations in a flow system.

A chemical titration procedure for both Cl and Br atoms has been developed and has been used to test an isothermal calorimetric detector which can measure the atom concentration along a reaction tube. The detector was used to establish the surface recombination coefficient (γ) for chlorine atoms (4×10^{-5}) and bromine atoms (6×10^{-5}) on oxyacid-covered surfaces.

INTRODUCTION

The electrical discharge has proved a valuable source of hydrogen, nitrogen, and oxygen atoms. In the last few years many of the species produced in the discharge have been identified. In addition, a variety of methods of following the concentration of the atomic species in a flow system have been described (1, 2, 3, 4). As a result, rate constants for a large number of elementary reactions of these atoms are being reported in the literature. Unfortunately, workers have had less success with halogen atoms in a flow system. The statement made in 1933 by Schwab (5) that bromine atoms recombine on every collision with the walls, and chlorine atoms survive fewer than 20 collisions irrespective of the wall materials, seems to have discouraged further work with these species in a flow system.

Recent developments in the theory of atom recombination (6, 7) point to the need for a system capable of studying the low pressure recombination of halogen atoms. In addition, there remain a considerable number of elementary halogen atom reactions which are in need of direct measurements. For this reason we have re-examined the possibility of obtaining halogen atoms in a flow system.

EXPERIMENTAL

Chemicals

Matheson Company chlorine was dried with silica gel and purified by distillation. Reagent grade bromine was dried with phosphorus pentoxide, and purified by distillation. Air was removed from reagent grade iodine by sublimation in vacuum. NOCl from Matheson Company was purified only by trap-to-trap distillation. All other gases and chemicals were of reagent grade purity and were used without purification.

Apparatus

A conventional pyrex flow system with a linear flow velocity between 100 and 400 cm per sec was used. Inert gas flows were controlled with Edwards needle valves, and measured with conventional capillary-U-tube flow meters. All mercury was isolated with a layer of octyl phthalate. Cl_2, Br_2, NOCl, and ICl gases were contained in 22-liter bulbs. A constant pressure was maintained with the appropriate freezing bath. Flow was controlled by glass capillaries only, and measured with H_2SO_4-filled flow meters. All stopcocks in the halogen flow system were greased with Kel-F grease.

[1]*Manuscript received August 18, 1961.*
Contribution from the Department of Chemistry, University of British Columbia, Vancouver 8, B.C.

The discharge tube and reaction tube are shown in Fig. 1. The discharge tube was constructed of quartz to prevent breakage while the tube was being heated. It was made

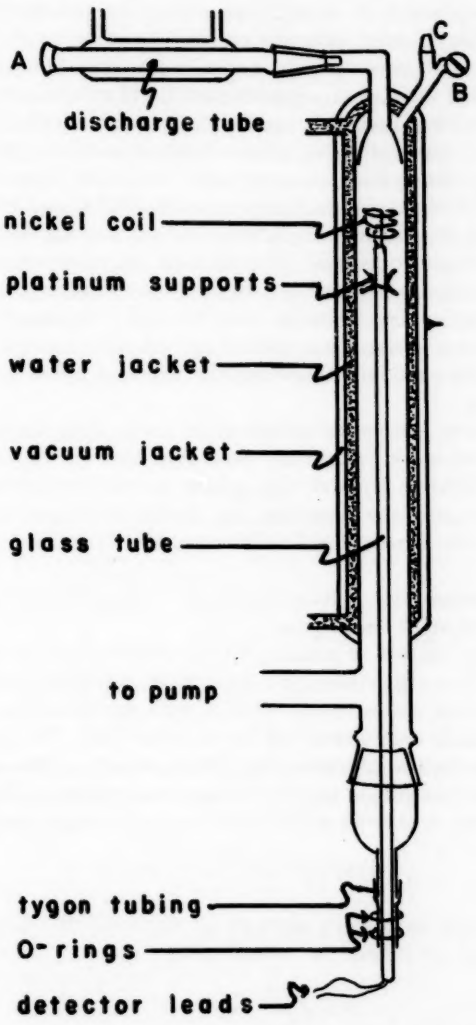

FIG. 1. Discharge tube, reaction tube, and movable detector assembly.

removable to facilitate cleaning since contamination occurred most often in this region. The jacket was used to cool the tube with a stream of air while the discharge was on. A 100-watt, 2450-megacycle generator was used to create the discharge.

The reaction tube was 50 cm long and had a diameter of 2.1 cm. It was surrounded by a water jacket for temperature control and a vacuum jacket to prevent a temperature gradient from forming when the tube is operated at other than room temperature.

The halogen gas (at flows between 0.5 and 45 μmoles/sec) could be introduced at A (Fig. 1) together with inert carrier gases such as argon and helium (at flows between 5 and 150 μmoles/sec). Other gases could be introduced after the discharge at B. Another opening at C made it possible to clean the reaction tube and apply different coatings to the reaction tube walls, without affecting the walls leading to the reaction tube. These coatings (hereafter called "poisons") were usually applied in the following manner. The cleaned vessel was filled with a hot, concentrated KOH solution and allowed to stand for 30 minutes. The vessel was then thoroughly washed with distilled water and filled with a 10% solution of the poison in water. This solution was allowed to stand for 1 hour and then drained. Finally, the system was evacuated for about 2 hours. During this period the discharge tube and reaction tube were heated to 250° C and 80° C respectively.

Figure 1 also shows the method which was used for moving both a coil of wire and a wrede gauge along the reaction tube. The movable vacuum-tight junction is provided by pressing a tygon tube against a glass tube with two O-rings. The glass tube is greased with Kel-F grease. No leaking occurred, and the slight degassing of the grease is of no consequence at this point in the flow system. The rack and pinion arrangement described previously (3) was also used for supporting the wire-coil but it cannot be used with a movable wrede gauge.

The principle of the isothermal–calorimetric atom detector (hereafter called the "detector") used in this work has already been described (3). It requires that the atoms in a gas stream recombine on a metal wire, raising its temperature to a value T. The heat liberated is then measured by observing the electrical current necessary to raise the wire temperature to the same value T. For successful operation the following requirements must be met:

(1) the thermal conductivity must be the same in the presence and absence of atoms;
(2) all the atoms must be recombined;
(3) no other species capable of heating up the detector can be present.

The first condition is easily satisfied in a gas simply subjected to an electrical discharge if the atoms recombine on almost every collision with the wire. The second condition can be satisfied by a suitable enlargement of the detector coil. The third condition can be verified by an independent atom measuring device which is insensitive to such species.

A wrede gauge was constructed with four 10-micron pinholes. The pressure difference across the pinholes was measured with an inclined oil-manometer.

RESULTS AND DISCUSSION

Fluorine

An attempt was made to pass F_2 through an electrical discharge. However, the gas was found too difficult to handle in a flow system and the experiment could not be completed.

Chlorine

Our first attempts to produce Cl atoms by passing a stream of the gas through a discharge in a pyrex and quartz tube were unsuccessful. A thin silver mirror which provides a sensitive test for halogen atoms by its discoloration showed no change 1 centimeter away from the discharge. Dry wall coatings of polythene, teflon, NaCl, NaOH, and $Al(OH)_3$ did not help to produce any detectable atoms.

On the other hand, when H_3PO_4, H_2SO_4, H_3AsO_4, H_3BO_3, and $HClO_4$ were used to "poison" the wall, immediate discoloration of the silver mirror occurred when the discharge was initiated. The absence and presence of atoms with these surface poisons was then verified with a wrede gauge. The atom concentrations measured with the gauge

were then compared with those measured by the detector using platinum, silver, cobalt, and nickel coils. The atom concentrations measured along the reaction tube by all methods were proportional to each other. However, the wrede gauge and platinum detector yielded a much lower value for the atom concentration than the Ag-, Co-, and Ni-covered detectors. The rapid atom recombination on the glass of the wrede gauge may account for the low value obtained with this instrument. A low catalytic activity for platinum has been observed previously (8) and would account for the low value obtained with this surface. Cobalt and silver detectors possess a number of other disadvantages. They are attacked by halogen atoms and the catalytic activity of the halide is somewhat lower than that of the metal. More troublesome, however, is the formation of some volatile compound that distills onto the walls at temperature above 100° C. Not only does nickel not possess these difficulties, but it also has a larger temperature coefficient of resistivity.

Complete removal of the atoms by the nickel coil was checked by placing a second detector immediately after the first. A 90-cm length of 30-gauge nickel wire wound into a double spiral and extended to a length of 1 cm was found to be effective in removing the atoms at pressures up to 4 mm Hg. At higher pressures it was difficult to prevent the atoms from being swept past the detector unless it was extended to about double this length.

Some typical chlorine atom flows measured 25 cm after the discharge are given in Table I.

TABLE I

Pressure, mm of Hg	Flow, in μmoles per second		
	Inert gas	Cl_2	Cl
2	50	1.5	1.5
2	50	7.0	2.5
0.4	5	10	4
0.5	5	20	8
0.6	5	30	10

Chemical Titrations

Chemical titration of oxygen and nitrogen atoms has been facilitated by the fact that many of these reactions are accompanied by light emission. Both reactions commonly used for nitrogen and oxygen atoms

$$N + NO \rightarrow N_2 + O$$

and

$$O + NO_2 \rightarrow NO + O_2$$

make use of the light-emitting reaction

$$O + NO \rightarrow NO_2 + h\nu$$

to observe the equivalence point of the titration. We have not found any useful light-emitting reaction in our work with halogen atoms, and hence a different equivalence indicator must be used.

We have found the following reaction most useful for titration of chlorine atoms:

$$Cl + NOCl \rightarrow NO + Cl_2.$$

Subsequent reactions

$$Cl + NO + M \rightarrow NOCl + M$$

$$Cl_2 + 2NO \rightarrow 2NOCl$$

are considerably slower under conditions present in the flow system. Figure 2 gives the atom flow measured by the detector as a function of the NOCl flow introduced through

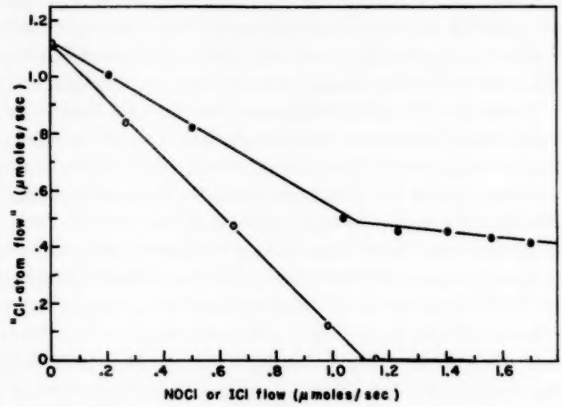

FIG. 2. Chlorine atom titration curves with NOCl (open circles) and with ICl (closed circles).

stopcock B in Fig. 1. The detector was placed 2 centimeters beyond the NOCl inlet. The agreement between the original chlorine atom flow measured by the detector and the NOCl flow necessary to remove all the atoms is excellent.

The titration of chlorine atoms with NOCl was carried out over a variety of experimental conditions. The technique used was to set the NOCl flow at some value in excess of the chlorine atom flow and then decrease the NOCl flow until atoms began to reach the detector. This NOCl flow was then recorded as the chlorine atom flow measured by titration. In all experiments carried out at a total pressure below 4 mm Hg the atom concentration measured by the two methods did not differ by more than 5%. However, the detector readings fell below those of the NOCl titration at higher pressures. This confirms the previous observation that at the higher pressures atoms are swept by the detector without being recombined.

It should be emphasized that though the detector is being used in the titration, the method is still an independent quantitative measurement. This is underlined by the fact that a glass-covered thermistor probe is even more effective in observing the end point of the titration.

Surface Recombination

With the nickel detector, the atom concentration was measured along the reaction tube. At a total pressure not greater than 0.3 mm Hg (due mostly to the carrier gas) the gas phase recombination is slow and can easily be corrected for. Though not unequivocally determined, the wall reaction appears to be of first order in chlorine atoms and can be written

$$\mathrm{Cl} + \text{wall} \xrightarrow{k_w} 1/2\,\mathrm{Cl_2} + \text{wall}$$

for which we have calculated a value of 0.8 $\mathrm{sec^{-1}}$ for k_w at 10° C with all the oxyacids used. The more meaningful recombination coefficient (γ), therefore, has a value of about 4×10^{-5}.

A considerably greater value was obtained until the marked effect of a small amount of water from the surface poison in the discharge was noted. The water not only greatly

increased the atom concentration but also caused a sharp increase in the rate of recombination of the atoms.

Bromine

The experiments described in the previous section were repeated with bromine. The results may be summarized as follows:

(1) No bromine atoms were detected in a stream of electrically discharged bromine unless the surfaces were coated with one of the oxyacids used for chlorine atoms.

(2) Bromine atoms can also be titrated with NOCl by the same technique used for chlorine atoms. The agreement between the atoms measured by titration and those measured with a nickel detector was satisfactory below a total pressure of about 4 mm Hg.

(3) Water vapor increases both the bromine atoms obtained from the discharge and the rate at which they are removed by recombination.

(4) The value of the surface recombination coefficient (γ) was found to be about 6×10^{-5} at 10° C for all the oxyacids used as surface poisons.

Iodine

To date we have had no success in obtaining iodine atoms from electrically discharged I_2. The difficulty seems to lie in the hot region immediately after the discharge because we have found that the atoms can be maintained if they are created outside the discharge.

The closed circles in Fig. 2 give the pseudo-chlorine atom concentration obtained when ICl is added to the same stream of chlorine atoms used in the NOCl titration. The fast reaction occurring is

$$Cl + ICl \rightarrow Cl_2 + I.$$

Subsequent reactions of iodine atoms are somewhat slower. The break in the curve probably represents the complete titration of chlorine atoms. This point is in reasonable agreement with the end point of the NOCl titration. Beyond this point on the curve the detector must be obtaining its heat from the recombination of iodine atoms. The fact that the heat obtained at the end point is not 36/58 of that originally obtained from the chlorine atoms may be due to the more rapid gas phase recombination of iodine atoms, which could be observed by moving the detector along the tube. This rapid gas phase recombination made it too difficult to estimate the wall recombination rate. Nevertheless, it is apparent that the absence of atoms from electrically discharged iodine vapor must be due to an even more rapid recombination in the hot region of the discharge.

CONCLUSION

The isothermal calorimetric detector has been shown to be capable of measuring accurately the concentration of both chlorine and bromine atoms in a flow system operating in the pressure range from 0.3 mm Hg to 4 mm Hg. The wall recombination coefficient (γ) has been shown to be sufficiently small to allow the use of this halogen atom source for kinetic studies. A number of reactions have been studied with this flow system and will be presented elsewhere.

ACKNOWLEDGMENTS

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β-AROYL-α- AND -β-ARYLPROPIONIC ACIDS

PART I. THEIR PREPARATION AND LACTONIZATION[1]

SAYED SHERIF

ABSTRACT

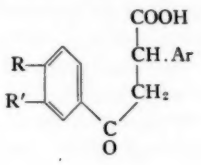
Bromobenzene reacts with phenyl- and *p*-methoxyphenyl-succinic anhydride in the presence of anhydrous aluminum chloride to give a mixture of *β-p*-bromobenzoyl-*α*- and -*β*-phenylpropionic acid, and a mixture of *β-p*-bromobenzoyl-*α*- and -*β-p*-hydroxyphenylpropionic acid, respectively.

Similarly, iodobenzene reacts with the same anhydrides to give a mixture of *β-p*-iodobenzoyl-*α*- and -*β*-phenylpropionic acid and *β*-benzoyl-*α*- and -*β*-phenylpropionic acid, and a mixture of *β*-benzoyl- and *β-p*-iodobenzoyl-*α-p*-methoxyphenylpropionic acid, respectively.

Phenyl- and diphenyl-succinic anhydride are cyclized by aluminum chloride to 1-ketoindane- and 1-keto-2-phenylindane-3-carboxylic acid, respectively.

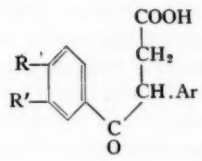
The above keto acids are converted by boiling acetic anhydride into *β,γ*-unsaturated *γ*-lactones.

Condensation of phenylsuccinic anhydride with bromobenzene in the presence of anhydrous aluminum chloride gave rise to a mixture of *β-p*-bromobenzoyl-*α*- and -*β*-phenylpropionic acid (I*a* and II*a*, respectively) in which the latter was predominant. The structure of the *α*-phenyl isomer was established by comparison with an authentic specimen prepared after Allen, Normington, and Wilson (1). The structure of the *β*-phenyl isomer was established by elemental analysis and by the production of *p*-bromobenzoic acid on oxidation with alkaline potassium permanganate. The reaction mixture contained a neutral product which was proved to be *p*-dibromobenzene, probably produced by the action of aluminum chloride on bromobenzene.



I

(*a*) R = Br; R′ = H; Ar = C_6H_5
(*b*) R = Br; R′ = H; Ar = *p*-HOC_6H_4
(*c*) R = I; R′ = H; Ar = C_6H_5
(*d*) R = R′ = H; Ar = C_6H_5
(*e*) R = R′ = H; Ar = *p*-$CH_3OC_6H_4$
(*f*) R = I; R′ = H; Ar = *p*-$CH_3OC_6H_4$
(*g*) R = R′ = Cl; Ar = C_6H_5
(*h*) R = R′ = Cl; Ar = H



II

(*a*) R = Br; R′ = H; Ar = C_6H_5
(*b*) R = Br; R′ = H; Ar = *p*-HOC_6H_4
(*c*) R = I; R′ = H; Ar = C_6H_5
(*d*) R = R′ = H; Ar = C_6H_5

When phenylsuccinic anhydride was replaced by *p*-methoxyphenylsuccinic anhydride, a mixture of *β-p*-bromobenzoyl-*α*- and -*β-p*-hydroxyphenylpropionic acid (I*b* and II*b*, respectively) was produced in which the latter was predominant. The structure of the *α-p*-hydroxyphenyl isomer was established by its identity with an authentic specimen prepared from *p*-bromophenyl 4-methoxystyryl ketone. The presence of the hydroxyl group was established by its infrared spectrum (see Experimental). The structure of the *β-p*-bromobenzoyl-*β-p*-hydroxyphenylpropionic acid was established by elemental analysis and by oxidation to *p*-bromobenzoic acid.

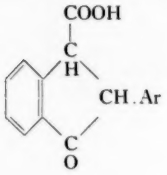
[1]*Manuscript received June 13, 1961.*
Contribution from the National Research Centre, Dokki, Cairo, Egypt, U.A.R.

The condensation of phenylsuccinic anhydride with iodobenzene under the same conditions gave a mixture of β-*p*-iodobenzoyl-α- and -β-phenylpropionic acid (I*c* and II*c*, respectively) and β-benzoyl-α- and β-phenylpropionic acid (I*d* and II*d*, respectively). The structure of the first acid was established by comparison with an authentic specimen prepared from *p*-iodophenyl styryl ketone. The structure of the second acid was inferred from its elemental analysis, and from the fact that it gave, on oxidation with alkaline potassium permanganate, *p*-iodobenzoic acid. The structure of the halogen-free acids was established by comparison with authentic specimens (2). The formation of the halogen-free acids is due to the partial dehalogenation of iodobenzene to benzene, under the experimental conditions, and not to the partial dehalogenation of the β-aroylpropionic acids for the following reasons: (i) *o*- and *p*-diiodobenzene were isolated from the reaction mixture, and from a mixture of aluminum chloride and iodobenzene treated under the same conditions, and (ii) β-*p*-iodobenzoyl-α-phenylpropionic acid was recovered unchanged, when heated with aluminum chloride in toluene at 100° for 3 hours.

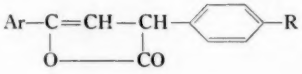
p-Methoxyphenylsuccinic anhydride reacted with iodobenzene in the presence of aluminum chloride to give a mixture of acids, which, after methylation and hydrolysis, was separated into β-benzoyl-α-*p*-methoxyphenylpropionic acid and β-*p*-iodobenzoyl-α-*p*-methoxyphenylpropionic acid (I*e* and I*f*, respectively); the former acid predominated. The structure of both acids was established by comparison with authentic specimens.

β-3,4-Dichlorobenzoyl-α-phenylpropionic acid (I*g*) was prepared by the addition of hydrogen cyanide to 3,4-dichlorophenyl styryl ketone and subsequent alcoholysis and hydrolysis of the corresponding nitrile.

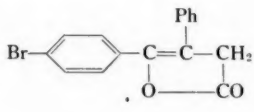
In the presence of aluminum chloride, succinic anhydride condensed with *o*-dichlorobenzene to give β-3,4-dichlorobenzoylpropionic acid (I*h*), the structure of which was established by oxidation with alkaline potassium permanganate to 3,4-dichlorobenzoic acid. However, under the same experimental conditions, phenylsuccinic anhydride failed to condense with *o*-dichlorobenzene, and instead it cyclized intramolecularly, giving 1-ketoindane-3-carboxylic acid (III*a*); this on decarboxylation gave α-hydrindone. Under the same conditions, α,β-diphenylsuccinic anhydride cyclized intramolecularly tc give 1-keto-2-phenylindane-3-carboxylic acid (III*b*), the structure of which was established by comparison with an authentic specimen (3).



III



IV



V

(*a*) Ar = H
(*b*) Ar = C_6H_5

When the β-aroyl-α- and -β-arylpropionic acids were boiled with acetic anhydride, they were converted to the corresponding β,γ-unsaturated γ-lactones (4, 5) (IV and V, respectively). The lactone structure was established by the appearance of its characteristic stretching frequency (6, p. 153) in the infrared spectra of these compounds (see Experimental).

The results of the present investigation agree with those of Baddar and Sherif (4).

EXPERIMENTAL

Melting points are uncorrected. Infrared spectra were measured with a Perkin–Elmer Infracord spectrophotometer Model 137, using the potassium bromide wafer technique.

β-p-Bromobenzoyl-α-phenylpropionic Acid

A mixture of β-*p*-bromobenzoyl-α-phenylpropionitrile (7) (20 g), ethanol (150 ml), and concentrated sulphuric acid (30 ml) was refluxed for 6 hours on a steam bath. The ester (22 g), which solidified on being cooled, was filtered off and crystallized from light petroleum (b.p. 50–70°) to give ethyl β-*p*-bromobenzoyl-α-phenylpropionate in colorless crystals, m.p. 70–71°. Calc. for $C_{18}H_{17}BrO_3$: C, 59.85; H, 4.74; Br, 22.13. Found: C, 59.83; H, 4.61; Br, 22.00.

The ester (20 g) was hydrolyzed with 10% aqueous potassium hydroxide (200 ml) (1 hour reflux) to give β-*p*-bromobenzoyl-α-phenylpropionic acid (17 g) (from benzene), m.p. 160–161°; Allen and co-workers (1) give the same melting point. Calc. for $C_{16}H_{13}BrO_3$: C, 57.69; H, 3.93; Br, 24.00. Found: C, 57.85; H, 4.00; Br, 23.73.

When the acid was treated with 2,4-dinitrophenylhydrazine in a warm mixture of ethanol and concentrated sulphuric acid, it gave the 2,4-dinitrophenylhydrazone of the ethyl ester in orange-yellow crystals (from dilute acetic acid), m.p. 161–162°. Calc. for $C_{24}H_{21}BrN_4O_6$: C, 53.24; H, 3.91; N, 10.35. Found: C, 53.22; H, 3.75; N, 10.15.

Condensation of Bromobenzene with Phenylsuccinic Anhydride

A solution of phenylsuccinic anhydride (17.6 g, 0.1 mole) in bromobenzene (20 ml) was added gradually to a well-cooled and stirred mixture of anhydrous aluminum chloride (26.7 g, 0.2 mole) and bromobenzene (30 ml). The reaction mixture was heated at 100° for 3 hours, decomposed with ice-cold dilute hydrochloric acid, and the solvent was steam-distilled. The product (20 g, 60% yield), m.p. 85–100°, was crystallized from the least amount of glacial acetic acid, then from ether, to give β-*p*-bromobenzoyl-β-phenylpropionic acid (16 g, 48% yield) in colorless crystals, m.p. 156–157°, depressed to 130–140° when admixed with the α-phenyl isomer. Calc. for $C_{16}H_{13}BrO_3$: C, 57.69; H, 3.93; Br, 24.00. Found: C, 57.90; H, 3.83; Br, 24.00.

On oxidation with alkaline potassium permanganate (1 hour at 100°), it gave *p*-bromobenzoic acid, m.p. and mixed m.p. 250°.

The acetic acid mother liquor was diluted with water, and the precipitated solid was crystallized from benzene to give β-*p*-bromobenzoyl-α-phenylpropionic acid (2 g, 6% yield), m.p. and mixed m.p. 160–161°.

The steam-distillable fraction was dried (Na_2SO_4) and fractionally distilled to give mainly bromobenzene and *p*-dibromobenzene, m.p. and mixed m.p. 89°.

Action of Aluminum Chloride on Bromobenzene

Aluminum chloride was added to cold bromobenzene. The reaction mixture was kept at 25–30° for 3 days and then decomposed and worked up as usual to give bromobenzene and *p*-dibromobenzene.

β-p-Bromobenzoyl-α-p-methoxyphenylpropionitrile

To a solution of *p*-bromobenzoyl 4-methoxystyryl ketone (8) (5 g) in ethanol (150 ml), glacial acetic acid (2.3 ml) and aqueous potassium cyanide (3.5 g in 9 ml water) were added. The reaction mixture was kept at 60–65° for 5 hours, then left overnight. The nitrile (4 g) had m.p. 132–133° (from ethanol), depressed to 115–120° on admixing with the above chalcone. Calc. for $C_{17}H_{14}BrNO_2$: C, 59.31; H, 4.10; Br, 23.21; N, 4.07. Found: C, 59.20; H, 4.16; Br, 22.86; N, 4.00.

β-p-Bromobenzoyl-α-p-methoxyphenylpropionic Acid

A mixture of the above nitrile (4 g), methanol (50 ml), and concentrated sulphuric acid (7 ml) was refluxed for 8 hours and the product (4 g) crystallized from methanol to give methyl β-*p*-bromobenzoyl-α-*p*-methoxyphenylpropionate in colorless crystals, m.p. 79–80°. Calc. for $C_{18}H_{17}BrO_4$: C, 57.31; H, 4.55; Br, 21.18. Found: C, 57.11; H, 4.42; Br, 21.10.

The ester was hydrolyzed by refluxing for 2.5 hours with 5% aqueous potassium hydroxide (100 ml). The reaction mixture was cooled, acidified, and the precipitated acid was crystallized from ethanol to give β-*p*-bromobenzoyl-α-*p*-methoxyphenylpropionic acid (3.5 g) in colorless crystals, m.p. 134–135°. Calc. for $C_{17}H_{15}BrO_4$: C, 56.22; H, 4.17; Br, 22.02. Found: C, 56.00; H, 4.20; Br, 22.00.

When the acid was warmed with 2,4-dinitrophenylhydrazine in ethanol and concentrated sulphuric acid, and the product was crystallized from acetic acid, the 2,4-dinitrophenylhydrazone of the ethyl ester was obtained, in yellow crystals, m.p. 188–189°. Calc. for $C_{25}H_{23}BrN_4O_7$: C, 52.55; H, 4.06; Br, 14.00; N, 9.81. Found: C, 52.41; H, 3.91; Br, 14.20; N, 10.08.

β-p-Bromobenzoyl-α-p-hydroxyphenylpropionic Acid

A mixture of β-*p*-bromobenzoyl-α-*p*-methoxyphenylpropionic acid (2.5 g), aluminum chloride (5 g), and bromobenzene (20 ml) was stirred at 100° for 2 hours, then worked up as usual. The product (2 g) was crystallized from ether to give β-*p*-bromobenzoyl-α-*p*-hydroxyphenylpropionic acid, in colorless crystals, m.p. 171–172°. It gave a deep blue color with warm concentrated sulphuric acid. Calc. for $C_{16}H_{13}BrO_4$: C, 55.05; H, 3.75; Br, 22.90. Found: C, 55.16; H, 3.75; Br, 22.90. Its infrared spectrum showed two bands at 3450 and 1670 cm^{-1} characteristic of a bonded OH group (6, p. 84) and the CO group of the aroyl group (6, p. 114), respectively.

p-Methoxyphenylsuccinic Anhydride

It was prepared from the acid (9) by refluxing with 3 times its weight of acetyl chloride for 6 hours. The excess of acetyl chloride was distilled off, and the residue fractionated, b.p. 205–208° at 5 mm (80% yield).

Condensation of Bromobenzene with p-Methoxyphenylsuccinic Anhydride

A solution of *p*-methoxyphenylsuccinic anhydride (20.6 g, 0.1 mole) in bromobenzene (40 ml) was gradually added to a well-cooled and stirred mixture of aluminum chloride (26.7 g, 0.2 mole) and bromobenzene (50 ml). The reaction mixture was left overnight, heated at 100° for 3 hours, then worked up as usual. The product (20 g, 57% yield) was crystallized from ether to give β-*p*-bromobenzoyl-β-*p*-hydroxyphenylpropionic acid, in colorless crystals, m.p. 198–199° (12 g, 34% yield), depressed to 150–155° when admixed with β-*p*-bromobenzoyl-α-*p*-hydroxyphenylpropionic acid. Calc. for $C_{16}H_{13}BrO_4$: C, 55.05; H, 3.75; Br, 22.90. Found: C, 55.32; H, 3.90; Br, 22.45. It gave a yellowish-green color with concentrated sulphuric acid. On oxidation with alkaline potassium permanganate, it gave *p*-bromobenzoic acid.

Concentration of the ether mother liquor gave β-*p*-bromobenzoyl-α-*p*-hydroxyphenylpropionic acid (6 g, 17% yield), m.p. and mixed m.p. 171–172°.

β-p-Iodobenzoyl-α-phenylpropionitrile

To a solution of *p*-iodophenyl styryl ketone (10) (3 g) in ethanol (75 ml), glacial acetic acid (2.3 ml) and aqueous potassium cyanide (3.5 g in 10 ml water) were added. The

reaction mixture was kept at 70–75° for 4 hours, then left overnight. β-*p*-Iodobenzoyl-α-phenylpropionitrile (3 g) was crystallized from ethanol in colorless crystals, m.p. 148–149°. Calc. for $C_{16}H_{12}INO$: C, 53.21; H, 3.35; I, 35.15; N, 3.88. Found: C, 53.11; H, 3.45; I, 34.76; N, 3.80.

β-p-Iodobenzoyl-α-phenylpropionic Acid

A mixture of the above nitrile (2 g), methanol (25 ml), and concentrated sulphuric acid (5 ml) was refluxed on a steam bath for 8 hours. The reaction mixture was diluted with water and the precipitated methyl β-*p*-iodobenzoyl-α-phenylpropionate (2 g) was crystallized from methanol, in colorless crystals, m.p. 132–133°, depressed to 115–120° when admixed with the corresponding nitrile. Calc. for $C_{17}H_{15}IO_3$: C, 51.79; H, 3.84; I, 32.20. Found: C, 51.70; H, 3.77; I, 32.00.

The preceding ester was hydrolyzed by refluxing for 1.5 hours with 5% aqueous potassium hydroxide (100 ml) to give β-*p*-iodobenzoyl-α-phenylpropionic acid (1.7 g), which was crystallized from ether in colorless crystals, m.p. 155–156°. Calc. for $C_{16}H_{13}IO_3$: C, 50.55; H, 3.45; I, 33.40. Found: C, 50.37; H, 3.60; I, 33.15. Oxidation of the α-phenylpropionic acid with aqueous alkaline potassium permanganate gave *p*-iodobenzoic acid, m.p. and mixed m.p. 270° (11).

Condensation of Iodobenzene with Phenylsuccinic Anhydride

The product from iodobenzene (60 ml), phenylsuccinic anhydride (17.6 g, 0.1 mole), and aluminum chloride (26.7 g, 0.2 mole) (3 hours at 100°) was extracted with boiling aqueous sodium carbonate solution. The extract, on being cooled and acidified, gave a semisolid residue (15 g). This was extracted several times with light petroleum (b.p. 50–70°), and the insoluble portion was crystallized from benzene to give β-benzoyl-β-phenylpropionic acid (2 g), m.p. and mixed m.p. 168° (2). Concentration of the benzene mother liquor gave β-benzoyl-α-phenylpropionic acid (3 g), m.p. and mixed (2) m.p. 154°. Evaporation of the benzene layer gave a semisolid residue which was crystallized several times from light petroleum (b.p. 70–90°) to give β-*p*-iodobenzoyl-β-phenylpropionic acid (2 g, 5.3% yield) in colorless crystals, m.p. 160–161°, depressed to 130–135° when admixed with its α-phenyl isomer. Calc. for $C_{16}H_{13}IO_3$: C, 50.55; H, 3.45; I, 33.40. Found: C, 50.82; H, 3.60; I, 32.47. Oxidation of the β-phenylpropionic acid with alkaline potassium permanganate gave *p*-iodobenzoic acid.

The light petroleum mother liquor was evaporated and the residue left was crystallized from ether to give β-*p*-iodobenzoyl-α-phenylpropionic acid (1.5 g, 4% yield), m.p. and mixed m.p. 156°.

The residue insoluble in sodium carbonate solution was dissolved in hot ethanol, and the oil and crystals, which were precipitated when the solution was cooled, were mechanically separated. The crystals, after crystallization from light petroleum (b.p. 50–70°), melted at 128°, not depressed when admixed with an authentic specimen of *p*-diiodobenzene. The oil was distilled under vacuum, b.p. 153–155° at 15 mm, and the solidified product was crystallized from light petroleum (b.p. below 40°) to give *o*-diiodobenzene in plates, m.p. and mixed m.p. 27° (12).

Action of Aluminum Chloride on β-p-Iodobenzoyl-α-phenylpropionic Acid

The acid (2 g) was dissolved in toluene (15 ml) and the cooled mixture was treated with aluminum chloride (5 g); the reaction mixture was stirred at 100° for 3 hours, then decomposed as usual. β-*p*-Iodobenzoyl-α-phenylpropionic acid was recovered unchanged, m.p. and mixed m.p. 156°.

Action of Aluminum Chloride on Iodobenzene

Iodobenzene was cooled to 0–5° and treated gradually with aluminum chloride. The reaction mixture was kept at room temperature (25–30°) for 3 days, then decomposed in the usual manner. *p*-Diiodobenzene and *o*-diiodobenzene were isolated from the reaction mixture as already mentioned.

p-Iodophenyl 4-Methoxystyryl Ketone

A mixture of *p*-iodoacetophenone (13) (18.4 g), ethanol (175 ml), water (60 ml), sodium hydroxide (7.5 g), and anisaldehyde (10.2 g) was stirred at 20–25° for 1.5 hours. *p*-Iodophenyl 4-methoxystyryl ketone (27 g) was obtained from ethanol in pale yellow crystals, m.p. 172–173°. Calc. for $C_{16}H_{13}IO_2$: C, 52.77; H, 3.60; I, 34.86. Found: C, 52.55; H, 3.51; I, 34.52.

β-p-Iodobenzoyl-α-p-methoxyphenylpropionitrile

To a solution of the above chalcone (3 g) in ethanol (175 ml), acetic acid (2.3 ml) and aqueous potassium cyanide (3.5 g in 10 ml water) were added. The reaction mixture was kept at 70–75° for 4 hours, then left overnight. The crystalline precipitate (3 g) was collected and crystallized from ethanol to give *β-p*-iodobenzoyl-*α-p*-methoxyphenylpropionitrile in colorless crystals, m.p. 164–165°. Calc. for $C_{17}H_{14}INO_2$: C, 52.21; H, 3.60; N, 3.58. Found: C, 52.10; H, 3.70; N, 3.41.

β-p-Iodobenzoyl-α-p-methoxyphenylpropionic Acid

A mixture of the preceding nitrile (2 g), methanol (25 ml), and concentrated sulphuric acid (4 ml) was refluxed for 10 hours. The reaction mixture was poured onto ice water and the crude methyl ester was directly hydrolyzed with 10% aqueous potassium hydroxide (100 ml) (1-hour reflux) to *β-p*-iodobenzoyl-*α-p*-methoxyphenylpropionic acid (1 g) from ether, m.p. 156–157°. Calc. for $C_{17}H_{15}IO_4$: C, 49.75; H, 3.69; I, 30.95. Found: C, 50.00; H, 3.60; I, 30.84.

Condensation of Iodobenzene with p-Methoxyphenylsuccinic Anhydride

The product from iodobenzene (60 ml), *p*-methoxyphenylsuccinic anhydride (20.6 g, 0.1 mole), and aluminum chloride (26.7 g, 0.2 mole) (3 hours at 100°) was steam-distilled and the residue extracted with boiling 10% aqueous sodium carbonate solution. The extract, on acidification, gave a semisolid residue (10 g), which was methylated with methyl iodide, potassium carbonate, and acetone. Hydrolysis of the esters (5% aqueous potassium hydroxide) gave a semisolid mass which, after crystallization from benzene, gave *β*-benzoyl-*α-p*-methoxyphenylpropionic acid (6 g), m.p. and mixed (9) m.p. 158°. Evaporation of the benzene mother liquor gave a gummy acid which, on crystallization from ether, gave *β-p*-iodobenzoyl-*α-p*-methoxyphenylpropionic acid (2 g), m.p. and mixed m.p. 156–157°.

The steam-distillable fraction was dried (Na_2SO_4) and fractionally distilled to give iodobenzene and *o*- and *p*-diiodobenzene.

β-3,4-Dichlorobenzoylpropionic Acid

A stirred mixture of aluminum chloride (53.4 g, 0.4 mole) and *o*-dichlorobenzene (75 ml) was treated portionwise with a solution of succinic anhydride (20 g, 0.2 mole in 25 ml of *o*-dichlorobenzene). The reaction mixture was heated at 100° for 3 hours, then worked up as usual. *β*-3,4-Dichlorobenzoylpropionic acid (30 g, 61% yield) came down from ethanol in colorless crystals, m.p. 167–168°. Calc. for $C_{10}H_8Cl_2O_3$: C, 48.61; H, 3.26; Cl, 28.70. Found: C, 48.57; H, 3.11; Cl, 28.61. Oxidation of this acid with alkaline potassium permanganate gave 3,4-dichlorobenzoic acid, m.p. and mixed (14) m.p. 208–209°.

3,4-Dichlorophenyl Styryl Ketone

A mixture of 3,4-dichloroacetophenone (15) (9.5 g), ethanol (100 ml), water (40 ml), sodium hydroxide (5 g), and benzaldehyde (5.3 g) was stirred at 50–55° for 1 hour, then allowed to cool. 3,4-Dichlorophenyl styryl ketone (10 g) was obtained in pale yellow crystals, m.p. 116–117° (from ethanol). Bradsher and co-workers (16) and Lutz and co-workers (17) gave m.p. 112–113° and 110–112°, respectively. Calc. for $C_{15}H_{10}Cl_2O$: C, 65.03; H, 3.63; Cl, 25.60. Found: C, 64.73; H, 3.60; Cl, 25.00.

β-3,4-Dichlorobenzoyl-α-phenylpropionitrile

To a solution of the above chalcone (2 g) in ethanol (50 ml), acetic acid (2 ml) and aqueous potassium cyanide (2 g in 5 ml water) were added. The reaction mixture was heated to the boiling point, then left overnight. The nitrile (2 g) was crystallized from ethanol in colorless crystals, m.p. 119–120°, depressed to 105–110° when admixed with the corresponding chalcone. Calc. for $C_{16}H_{11}Cl_2NO$: C, 63.19: H, 3.65; Cl, 23.31; N, 4.60. Found: C, 63.00; H, 3.60; Cl, 23.11; N, 4.45.

β-3,4-Dichlorobenzoyl-α-phenylpropionic Acid

A mixture of the above nitrile (2 g), methanol (25 ml), and concentrated sulphuric acid (5 ml) was heated on a steam bath for 10 hours. The ester that precipitated on cooling was hydrolyzed with 5% aqueous potassium hydroxide (100 ml) (1.5 hours reflux) to give β-3,4-dichlorobenzoyl-α-phenylpropionic acid (1.5 g) as colorless crystals from methanol, m.p. 170–171°. Calc. for $C_{16}H_{12}Cl_2O_3$: C, 59.47; H, 3.74; Cl, 21.95. Found: C, 59.21; H, 3.75; Cl, 21.46.

1-Ketoindane-3-carboxylic Acid

Phenylsuccinic anhydride (17.6 g) in *o*-dichlorobenzene (20 ml) was added gradually to a well-cooled and stirred mixture of aluminum chloride (26.7 g) and *o*-dichlorobenzene (30 ml). The reaction mixture was heated at 100° for 2 hours, then worked up as usual. The colorless crystalline acid, m.p. 85° (from water), was dried in vacuum to give 1-ketoindane-3-carboxylic acid (12.5 g, 71% yield), m.p. and mixed (18) m.p. 120°.

α-Hydrindone

A mixture of 1-ketoindane-3-carboxylic acid (2 g), quinoline (15 ml), and copper bronze (0.5 g) was refluxed for 1 hour, cooled, and decomposed as usual. The reaction mixture was extracted with benzene. The removal of the solvent left an oil (ca. 1.5 g) which, on trituration with light petroleum (b.p. below 40°), gave colorless crystals, m.p. 42°; it was converted into α-hydrindone 2,4-dinitrophenylhydrazone, m.p. and mixed m.p. 260° (decomp.).

1-Keto-2-phenylindane-3-carboxylic Acid

A mixture of diphenylsuccinic anhydride (8.5 g) and aluminum chloride (10 g) in *o*-dichlorobenzene (30 ml) was heated at 100° for 2 hours, decomposed, and the solvent was steam-distilled. 1-Keto-2-phenylindane-3-carboxylic acid monohydrate (ca. 8 g) was crystallized from dilute ethanol in colorless crystals, m.p. and mixed (3) m.p. 116–117° (decomp.).

Lactonization of β-Aroyl-α- and -β-arylpropionic Acids

The solution of the acid (1 g) in acetic anhydride (10 ml) was refluxed for 2 hours and, after cooling, poured into water. The solid was filtered off and washed with dilute sodium carbonate solution. The lactone (ca. 100% yield) was then crystallized from a suitable solvent (see Table I).

TABLE I

Lactone							Analysis (%)					
							Calculated			Found		
No.	Ar	R	Solvent	M.p.	ν_{max}§ (cm^{-1})	Formula	C	H	Halogen	C	H	Halogen
IV	C_6H_5	OCH_3	C_6H_6–Pet†	107–108°	1750	$C_{17}H_{14}O_3$	76.68	5.31	—	76.44	5.30	—
IV	β-Naphthyl*	H	C_6H_6–Pet†	123–124°	1745	$C_{20}H_{14}O_2$	83.90	4.93	—	83.82	4.84	—
IV	2-Fluorenyl*	H	Ether	159–160°	1745	$C_{23}H_{16}O_2$	85.18	4.98	—	85.05	5.00	—
IV	p-Br·C_6H_4	H	C_6H_6	158–159°	1745	$C_{16}H_{11}BrO_2$	60.95	3.52	25.35	61.00	3.60	25.85
IV	p-Br·C_6H_4	OCH_3	C_6H_6–Pet†	149–150°	1755	$C_{17}H_{13}BrO_3$	59.16	3.80	23.15	59.04	3.64	22.93
IV	p-I·C_6H_4	H	C_6H_6	173–174°	1755	$C_{16}H_{11}IO_2$	53.07	3.06	35.05	53.41	3.22	34.57
IV	3,4-Cl_2·C_6H_3	H	C_6H_6	157–158°‡	1750	$C_{16}H_{10}Cl_2O_2$	63.00	3.30	23.25	63.40	3.25	22.84
V	—	—	C_6H_6	141–142°	1755 & 1786	$C_{16}H_{11}BrO_2$	60.95	3.52	25.35	61.01	3.51	24.54

*The corresponding keto acids were prepared after Hidayetulla and co-workers (19) and Baddar and his students (2), respectively.
†Pet = light petroleum (b.p. 50–70°).
‡Decomp.
§Stretching frequency for β,γ-unsaturated γ-lactones.

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THE CHEMICAL COMPOSITION OF THE WOOD AND BARK EXTRACTIVES OF JUNIPERUS HORIZONTALIS MOENCH[1]

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ABSTRACT

The wood of creeping juniper was found to contain about 10% acetone-soluble material. Of this, about one quarter was ligroin soluble and, from this portion, thujopsene, α-cedrene, cuparene, cedrol, widdrol, β-sitosterol, esters of fatty acids and β-sitosterol, the lignan savinin, and the recently discovered diterpene communic acid were isolated. Three unidentified hydrocarbons and several unknown alcohols and ketones were also obtained in small amounts. The ether-insoluble portion consisted of intractable polyphenolic material. The composition of the ligroin-soluble extract of the bark of this shrub resembled that of the wood in many respects. Neither the wood nor the bark extractives contained thujaplicins in detectable amounts.

Creeping juniper (*Juniperus horizontalis* Moench; also *Sabina horizontalis* (1)) is a prostrate shrub which is found widely distributed across Canada and occurs frequently in the dry, sandy regions of the Prairie Provinces. A survey of the literature did not reveal any reference to chemical investigations of the components of this plant. This paper deals with some of the components found in the wood and bark of the conifer.

The wood, after removal of the bark, was milled and extracted with acetone, giving 9–10% of soluble material. This extract was then fractionated into various groups of compounds as shown in Fig. 1. When the wood was extracted directly with ligroin, the same yield of ligroin-soluble material was obtained and this was divided into neutral, phenolic, and acidic material in the usual manner. The major portion consisted of neutral components which were fractionated by chromatography on a silicic acid column into five distinct classes of compounds: hydrocarbons, esters, mixed ketones and alcohols, sitosterol, and a lactone, respectively.

Hydrocarbons

The hydrocarbon fraction (0.22% of the weight of wood) was analyzed by gas–liquid chromatography (GLC) (2), which showed the presence of one major and five minor sesquiterpene hydrocarbons. The retention times of these components corresponded with six of the seven sesquiterpene hydrocarbons found in commercial cedar wood oil (from *Juniperus virginiana*). Runeberg (3) has identified three of these to be α-cedrene, thujopsene, and cuparene. The first peak recorded from the mixture from creeping juniper had the retention time and infrared spectrum of α-cedrene. The second and major constituent corresponded in retention time to either thujopsene or the isomer of cedrene (4) which is obtained when cedrol is dehydrated by the method of Motl *et al.* (5). This component was not attacked by cold, dilute permanganate solutions, nor did it yield any identifiable product on dehydrogenation with either selenium or palladized charcoal. On oxidation with selenium dioxide, a crystalline aldehyde, m.p. 71–72° C, was obtained. This, together with the GLC and infrared analysis, suggested the major hydrocarbon to be thujopsene. This was confirmed by oxidizing an authentic sample of thujopsene (kindly supplied by Prof. H. Erdtman and T. Norin, Stockholm, Sweden) with selenium dioxide to thujopsenal (6), m.p. 71.5–72° C, which showed no depression in melting point with

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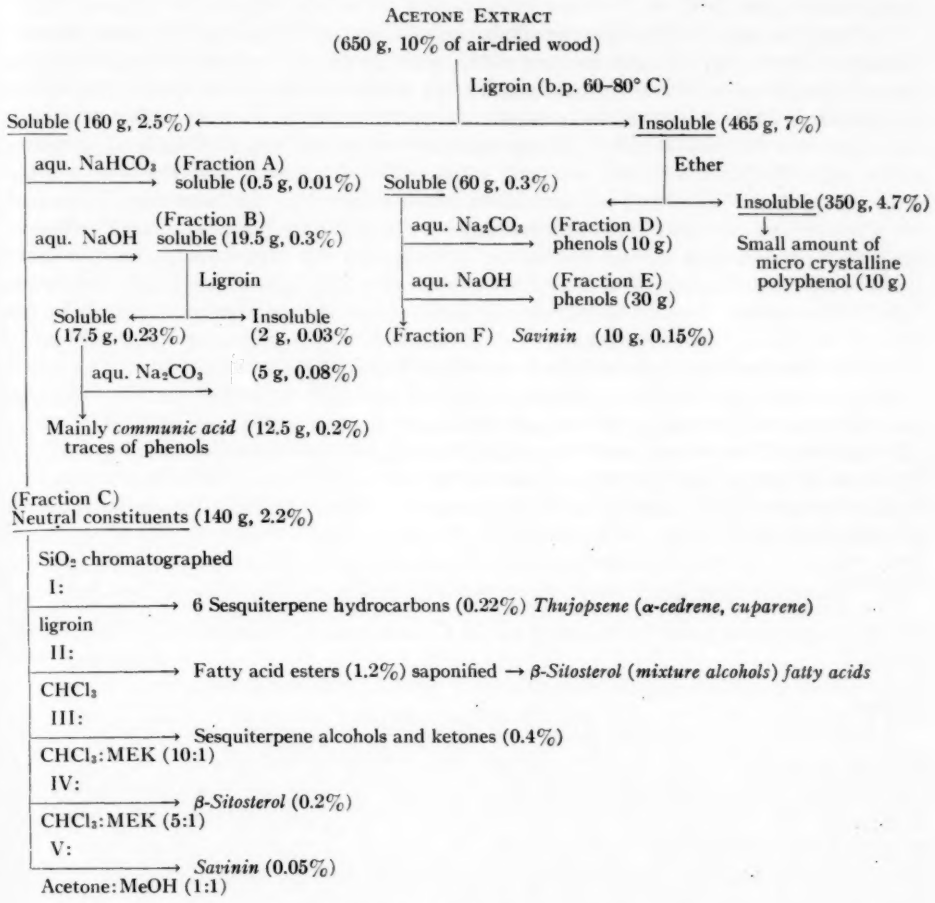

FIG. 1. Fractionation scheme for the wood extractives.

the above aldehyde. It was found that although thujopsene did not react with cold potassium permanganate solution, a liquid diol could be prepared from it with osmium tetroxide. Of the other minor hydrocarbons, none could be obtained pure. However, a concentrate of the second last peak gave an infrared spectrum resembling that of cuparene.

Esters

The ester fraction (1.2%) was saponified and from the non-saponifiable portion β-sitosterol and a small amount of a mixture of aliphatic alcohols were obtained. GLC analysis of the latter mixture showed two peaks in the C-12 range, one in the C-15, and one in the C-20 range. The acid portion consisted of a mixture of long-chain fatty acids which was analyzed by GLC (7). Peaks corresponding to palmitic, palmitoleic, stearic, oleic, linoleic, linolenic, and arachidic acid were recorded in the ratio of 6:1:1:13:37:6:2. The high proportion of the unsaturated C_{18} acids is typical for conifer wood (8).

Ketones and Alcohols

The third fraction (0.4%) from the silicic acid chromatogram was found to be a mixture of sesquiterpene alcohols and ketones. GLC analysis on the adipate polyester column showed the presence of two components having retention times corresponding to those of cedrol and widdrol, four minor constituents, and a major constituent with a very high retention time. Preparative GLC (20 mg scale) led to the isolation of milligram quantities of the cedrol–widdrol mixture, a mixed ketone–alcohol fraction, and the slow-moving major component. The cedrol–widdrol mixture was resolved on the polyester column and the identity of each alcohol was substantiated by its infrared spectrum. The identity of these two alcohols was further verified by dehydrating the mixture with the pyridine-modified alumina catalyst (4) to a product consisting mainly of α-cedrene and thujopsene (GLC). The second fraction had strong hydroxyl and carbonyl absorption bands in the infrared region. Re-chromatography of this fraction on the polyester column gave at least three peaks with strong indications that decomposition took place. The third fraction corresponded to the component having a very high retention time on the polyester column. Its infrared spectrum had absorption peaks at 1665 and 1618 cm^{-1}, and a maximum at 235 mμ with a weak shoulder 285 mμ was recorded in the ultraviolet region. Attempts to isolate and purify the ketones by means of Girard P reagent or column chromatography failed, mainly because of extensive decomposition of one or more of the components.

Sitosterol

Free β-sitosterol (0.016%) was obtained crystalline from the fourth fraction. No volatile constituents could be detected by GLC in the residue obtained from the mother liquors.

Lactone

Of more interest was the last fraction (0.05%) from the chromatogram which was also obtained in crystalline form. The purified, light yellow compound had m.p. 146–147°, $[\alpha]_D^{20}$ −82.3°, and a molecular weight of 362. The ultraviolet spectrum showed maxima at 237, 294, and 334 mμ, whereas the infrared spectrum (KBr disk and $CHCl_3$ solution) had two strong adsorption bands at 1740 and 1640 cm^{-1}, indicating the presence of an α,β-unsaturated lactone. The presence of a lactone ring was confirmed by the solubility of the compound in alcoholic alkali, from which the parent compound was recovered unchanged on acidification. The compound was insoluble in cold ethanol or cold aqueous alkali. Except for the position of the infrared bands discussed above, these data suggested a close resemblance with savinin. The structure of this lignan lactone was elucidated by Hartwell *et al.* (9, 10), who reported infrared absorption peaks at 1751 and 1651 cm^{-1} and also that the compound formed colorless crystals. The mixed melting point of authentic savinin (kindly supplied by Drs. J. L. Hartwell and A. W. Schrecker, Bethesda, U.S.A.) with the yellow compound isolated from creeping juniper was not depressed. The authentic sample also gave absorption bands at 1740 and 1640 cm^{-1} on the infrared spectrophotometer used in these experiments, and agreed in all other respects as well. Thus, there is no doubt that the two compounds are identical.

Acids and Phenols

The acidic portion of the ligroin- and ether-soluble extract was found to consist mainly of a diterpene acid (0.25%) $C_{20}H_{30}O_2$, m.p. 121–122° C, $[\alpha]_D^{25}$ +40.3°. On treatment with diazomethane the acid readily formed a methyl ester having m.p. 108–109° C, $[\alpha]_D^{25}$ +50.5°, which could not be saponified even at 125° C. GLC analysis showed the

methyl ester to be a single compound. The infrared spectrum showed the presence of a terminal methylene group (890 cm^{-1}) and a trisubstituted double bond (1645 and 795 cm^{-1}). Hydrogenation over platinum oxide catalyst resulted in the uptake of hydrogen equivalent to three double bonds. These data suggested that the acid was identical with the sirupy communic acid, isolated recently by Arya *et al.* from the wood of *Juniperus communis* L. (11). This was confirmed by preparing the maleic anhydride adduct of the ester, m.p. 170–171° C, $[\alpha]_D^{25}$ +79.5°. It is to be noted that in the preparation from *Juniperus horizontalis* the acid was obtained readily in the crystalline state.

Small amounts of phenolic materials were also obtained from the acidic portion. Paper chromatography (12) did not reveal the presence of any thujaplicins or related tropolones. This is surprising, since Runeberg and Pilo (13, 14) have found thujaplicins and nootkatin in a large number of juniper species. Thus, the extractives of creeping juniper wood more nearly resemble those of *Chamacyparis thyoides* (15), which are reported to contain no thujaplicins, but α-cedrene, cuparene, thujopsene, cedrol, widdrol, and carvacrol methyl ether. The finding of thujopsene, α-cedrene, cuparene, cedrol, widdrol, and communic acid does show, however, the close biogenetic relationship of the extractive components of creeping juniper with the other juniper species investigated.

The major portion (about 75%) of the acetone-soluble extractives of the wood of creeping juniper consisted of a brown, resinous phenolic material. Various fractionation attempts resulted only in the isolation of a small amount of microcrystalline polyphenolic material. The separation and identification of individual components from this so-called "phlobaphene" fraction will be studied further when more suitable fractionation techniques have been found.

Bark Extractives

It was of interest to determine whether the terpenoid compounds found in the wood could also be isolated from the bark of creeping juniper. The bark was milled to a fine powder, extracted with ligroin, and the extract was divided into neutral and acidic constituents. Column chromatography of the neutral portion gave as the first fraction hydrocarbons which appeared from GLC analysis to contain the same components as found in the corresponding fraction of the wood extractives. However, the component having the retention time of α-cedrene was present in about three times the amount of thujopsene. Treatment of the mixture with aqueous permanganate did not result in the formation of α-cedrene diol (16). Oxidation of the mixture with selenium dioxide produced a liquid aldehydic material in high yield which gave, on GLC analysis, only a peak corresponding to thujopsenal. Thus it may be that the unknown major hydrocarbon is an isomer of thujopsene rather than α-cedrene.

The second fraction from the column was composed of esters of β-sitosterol and a mixture of fatty acids. A mixed ketone–alcohol fraction was also isolated but GLC data showed that the individual components differed from those found in the same fraction obtained from the wood. In addition, an ester fraction was isolated which was composed of alcohols having terpenoid character and a mixture of C_{16}, C_{18}, and C_{20} acids in which the latter predominated. The alcoholic material could not be fractionated by column chromatography and characterization will be attempted by preparative GLC, once this technique has been perfected.

Savinin was isolated from the bark extract in small, though better, yield than was obtained from the wood. The major acidic component was again communic acid. Small amounts of untractable phenolic material were also obtained. Thus, the composition of the ligroin extract of the bark resembled that of the wood in many respects.

EXPERIMENTAL

Melting points were determined on a Leitz hot stage microscope. The identity of known compounds was confirmed by mixed melting point and by comparing the infrared spectra with those of authentic samples unless otherwise indicated. The infrared spectra were recorded on a Perkin–Elmer Model 21 double-beam recording spectrophotometer using the KBr-disk method, the film technique, or solutions in carbon tetrachloride. GLC chromatograms were obtained with a modified Beckman GC-2 chromatograph, using either 6 ft×¼ in. O.D. coiled copper columns packed with adipate (2) or succinate (7) polyester and "Chromosorb W" (80 to 100 mesh) in the ratio of 1:6, an 18 in.×¼ in. O.D. column containing washed silicone grease (2) on Celite (100 to 120 mesh) in the ratio of 1:6, or a 3 ft×¼ in. O.D. stainless steel column containing SE-30 silicone rubber (Dow Corning) on "Chromosorb W" (40 to 60 mesh) in the ratio of 1:3. The commercial cedar wood oil (Fritzsche Bros. of Canada Ltd., Toronto) used for comparison was obtained from the wood of *Juniperus virginiana* L.

Extraction of the Wood

The plants were collected near Saskatoon in the early fall of 1960 and in the spring of 1961. The leaves and bark were separated mechanically from the wood and the wood was milled to a fine powder by means of a hammer and a Wiley mill. The air-dried, milled wood (6.5 kg) was extracted continuously with acetone in a Soxhlet extractor for 24 hours and the extract was reduced to a brown, viscous sirup by distilling off most of the acetone. A small aliquot was evaporated to dryness to determine the yield of acetone-soluble material. The residue was poured into excess ligroin (b.p. 60–80° C) (4 liters) and the clear ligroin solution was decanted from the brown, resinous, insoluble material. The latter was washed twice with ligroin and the washings were added to the ligroin extract. The combined ligroin extract (6 liters) was concentrated to 2 liters by distillation. The yield of acetone-soluble material (650 g) was about 10% of the weight of air-dried wood, and that of the ligroin-soluble portion was 2.5%. The ligroin-soluble material could be obtained in about the same yield by extracting the milled wood directly with ligroin in a Soxhlet extractor.

Preliminary Fractionation

The concentrated ligroin extract (160 g in 2 liters) was extracted with a saturated solution of sodium bicarbonate and washed with water. The aqueous extracts were combined, acidified with cold dilute hydrochloric acid, and extracted with ether. The ethereal solution was dried over anhydrous sodium sulphate and after filtration evaporated to dryness to yield 0.5 g of a brown sirupy material (fraction A). The ligroin solution was then further extracted with two portions (100 ml) of aqueous sodium hydroxide solution (5%). The ligroin layer was again washed with water and the aqueous solutions pooled. The latter was acidified with cold, dilute hydrochloric acid, extracted with ether, and worked up as above to yield 19.5 g of weakly acidic material (fraction B). The residual ligroin solution was dried over anhydrous sodium sulphate and, after filtration, evaporated to dryness to yield 140 g of neutral oil (fraction C). When a small aliquot of the neutral material was distilled on a Widmer column, decomposition was encountered. About 20% of the material distilled between 110° and 140° C at 3 mm pressure. It was observed that chromatography on a silicic acid column, followed by vacuum distillation, gave a better separation of the volatile components.

Silicic Acid Column Chromatography

The neutral oil (10 g) in chloroform was chromatographed on a 2.0-cm diameter column of silicic acid (100 g) slurried in ligroin (b.p. 40–60° C). The column was eluted successively with ligroin (b.p. 40–60° C), chloroform, chloroform–2-butanone (10:1 and 5:1 v/v), and acetone–methanol (1:1 v/v), the solvent being changed when the last 50 ml of eluate gave no residue on evaporation. Five distinct fractions were collected in 1.2, 4.8, 1.6, 0.6, and 0.2 g amounts respectively. The infrared spectra showed the first to contain hydrocarbons, the second esters, the third a mixture of ketones and alcohols, the fourth alcohols, and the last a lactone.

Fraction I: Thujopsene and other Sesquiterpene Hydrocarbons

The material was analyzed by GLC on the adipate polyester column at 180° C. Six peaks were recorded in the sesquiterpene hydrocarbon range in 5, 72, 3, 6, 5, and 8% amounts respectively. The relative retention times (RRT; α-cedrene = 1.00) were 1.02, 1.15, 1.57, 1.74, 1.97, and 2.28 respectively. When commercial cedar wood oil, obtained from *Juniperus virginiana*, was injected, seven peaks were recorded, six of which corresponded in retention times to the above peaks. Fractional distillation gave a middle cut, b.p. 110–120° C (air bath) at 3 mm pressure, which contained about 88% of the major component. Found: C, 87.41%; H, 11.60%; n_D^{26} 1.5049; $[\alpha]_D^{26}$ −44.4 ($CHCl_3$). Calculated for $C_{15}H_{24}$: C, 88.16%; H, 11.84%. The crude hydrocarbon was unaffected by cold neutral or alkaline solutions of potassium permanganate. Selenium dehydrogenation (at 280 to 320° C) did not yield any identifiable product, nor was a crystalline picrate obtained. When the crude hydrocarbon was hydrogenated, using either palladized charcoal or platinum oxide as catalyst, the main hydrocarbon was recovered unchanged (GLC).

The crude hydrocarbon (300 mg), selenium dioxide (200 mg), and ethanol (30 ml) were heated under reflux for 4 hours. The ethanol was removed by evaporation under reduced pressure and ether was added to the residue. The ethereal solution was decanted from the residual selenium metal and the ether-soluble material (which contained appreciable amounts of selenium) was distilled *in vacuo* to give a pale yellow liquid, b.p. 110° C (air bath) at 3 mm pressure, which solidified partially on standing for some time. The distillate was taken up in ligroin (1 ml) and left at 2–5° C for several days, when the product crystallized in colorless, rectangular rods, m.p. 71–72° C after two recrystallizations. Found: C, 82.54%; H, 10.25%. Calculated for $C_{15}H_{22}O$: C, 82.51%; H, 10.16%. When an authentic sample of thujopsene was oxidized in the same manner thujopsenal of m.p. 71.5–72° C was obtained.

A few milligrams of the first peak were obtained almost pure by preparative GLC (20 mg scale) (2). The material had an infrared spectrum similar to that of α-cedrene. The presence of cuparene was inferred from the infrared spectrum of a concentrate of the second last peak, which was similar to that of this aromatic hydrocarbon.

Thujopsene diol.—Thujopsene (85% pure) (250 mg) and osmium tetroxide (250 mg) were dissolved in anhydrous ether (30 ml) and pyridine (1 ml). A brown, fluffy precipitate formed. The mixture was left at room temperature for 24 hours. It was then centrifuged, the solvent removed by decantation, and the solid residue was washed with ether. To the residue was added sodium bisulphite (1.5 g) in water (10 ml) and ethanol (30 ml), and the mixture was heated on a steam bath for 4 hours. The cooled solution was filtered and the alcohol was removed by evaporation *in vacuo*. The residual aqueous solution was extracted

repeatedly with ether and the ethereal extract was dried over anhydrous sodium sulphate. The oily residue obtained on evaporation of the ether contained no starting material (GLC) and showed a strong hydroxyl absorption band in the infrared region. The diol crystallized from ether–ligroin (1:1 v/v) at 2–5° C but liquefied immediately upon filtration, even in the cold.

Fraction II: Esters of β-Sitosterol, Aliphatic Alcohols, and Long-Chain Fatty Acids

This fraction was a viscous oil with a fatty odor. The infrared spectrum showed, as the only significant band, an ester carbonyl absorption (1740 cm^{-1}). The material was, therefore, saponified with alcoholic potassium hydroxide (steam bath, 2 hours) and worked up into the neutral and acidic components in the usual manner. Silicic acid chromatography of the neutral portion gave two distinct fractions. The first (10%) was analyzed by GLC on the silicone column at 160 and 200° C and was found to consist of four alcohols, two in the C-12, one in the C-15, and one in the C-20 range. The second fraction (90%) crystallized from acetone and was found to be β-sitosterol, m.p. 139–140° C, acetate m.p. 132–133° C. An aliquot of the acid portion was methylated with diazomethane and the mixture of methyl esters was analyzed by GLC on the succinate polyester column at 205° C. Peaks corresponding in retention time to palmitic (9.1%), palmitoleic (1.5%), stearic (1.5%), oleic (19.1%), linoleic (55.5%), linolenic (9.1%), and arachidic (3.03%) acids were recorded.

Fraction III: Mixed Alcohols and Ketones

Infrared analysis indicated that this fraction was composed of alcohols (3440 cm^{-1}) and ketones (1667 cm^{-1}). Found: C, 81.93%; H, 10.55%. Calculated for $C_{15}H_{24}O$: C, 81.76%; H, 10.98%. The mixture was analyzed by GLC, using the adipate polyester column at 180° C. Seven peaks were recorded in the ratio of 9:20:1:2:1:2:5:65. The respective RRT (cedrol = 1.00) were 1.02, 1.16, 1.44, 1.62, 1.94, 2.50, and 3.80. Some decomposition appeared to take place. Preparative runs of 20-mg aliquots on the SE-30 column yielded 5 to 10 mg each of three major components. These were re-chromatographed on the adipate polyester column, when the first fraction was resolved into two peaks corresponding in retention time to cedrol and widdrol. Sufficient material could be collected to record the infrared spectra of each component and these corresponded with those of cedrol and widdrol. The mixture (10 mg) was heated with alumina (30 mg) containing pyridine (1%) in a 5-mm glass tube (4) at 230° C for 1 hour. After it was cooled, the product was extracted with ether, and the ethereal solution was filtered and then evaporated to dryness. When the residue was chromatographed on the adipate polyester column, two major peaks, corresponding in retention time to α-cedrene and thujopsene, were recorded. The second fraction from the preparative run was found to decompose extensively on re-chromatographing on the polyester column; one major (RRT 1.62) and two minor peaks (RRT 1.44 and 1.94) were recorded but all were ill-defined. The infrared spectrum of the collected fraction showed strong absorption bands at 3360, 2900, 1675, (1650), 1460, and 1377 cm^{-1} and medium ones at 885, 875, 815, and 705 cm^{-1}. The ultraviolet spectrum showed a broad maximum at 245 mμ. The third fraction was composed of the component having RRT 3.80 on the polyester column. It had a weak infrared spectrum with absorption bands at 2960, 2925, 1665, 1618, 1455, 1435, 1387–1372, 1355, 1295–1285, 1200, and 885–870 cm^{-1}. Its ultraviolet spectrum showed a maximum at 235 mμ with a weak shoulder at 282 mμ.

Fraction IV: β-Sitosterol

This fraction crystallized on reducing the volume of solvent. Recrystallization from methanol gave white plates of β-sitosterol, m.p. 138–139° C, acetate m.p. 132–133° C.

Fraction V: Savinin

The yellow sirup obtained on evaporation of the solvent was taken up in acetonitrile and allowed to stand at 2–5° C for several days. A crystalline substance, m.p. 135–140° C, was obtained which was recrystallized twice from ethanol; m.p. 146–147° C, $[\alpha]_D^{25}$ −82.3° (*c*, 0.6, $CHCl_3$). Found: C, 68.50%; H, 4.75%; molecular weight (Rast), 362. Calculated for $C_{20}H_{16}O_6$: C, 68.18%; H, 4.58%; molecular weight, 352.

The compound is sparingly soluble in cold alcohol, insoluble in cold aqueous sodium hydroxide solution, and was recovered unchanged on acidifying an alcoholic solution containing sodium hydroxide. The ultraviolet spectrum showed maxima at 334, 294, and 237 mμ and minima at 306 and 266 mμ and alkaline solutions fluoresced strongly. The infrared spectrum had strong carbonyl absorption bands at 1740 and 1640 cm^{-1}. The position of these bands did not change on standardizing the infrared spectrophotometer against indene or polystyrene film. The authentic sample of savinin, m.p. 146.2–147.3° C, $[\alpha]_D^{22}$ −88.2°, also gave absorption bands at 1740 and 1640 cm^{-1} with the standardized instrument.

Acidic Components

Both the fractions obtained from the aqueous bicarbonate (fraction A) and sodium hydroxide solutions (fraction B) were investigated for the presence of tropolones. The paper chromatographic procedure of Wachtmeister and Wickberg (12) did not reveal any thujaplicins or nootkatin. A number of weak spots corresponding to phenols (ferric chloride color reaction) were obtained with butanol – acetic acid – water (4:1:2) as solvent.

The acid fraction B (see above) was triturated twice with ligroin (250 ml each) and the solution was decanted from the insoluble residue. The solution was extracted with aqueous sodium carbonate solution. The alkaline solution was separated, acidified with dilute hydrochloric acid, and extracted with ether. The ethereal solution was dried, filtered, and evaporated. The residue (5.0 g) was chromatographed on a column of silicic acid when three distinct fractions were collected. Paper chromatography again showed the absence of tropolones.

The carbonate-extracted ligroin solution was dried over anhydrous sodium sulphate and, after filtration, evaporated to dryness. The residue (17.5 g) was chromatographed on silicic acid. The major portion was eluted with ligroin (b.p. 40–60° C) and the residue obtained on evaporating the solvent (12.5 g) crystallized from acetone–ligroin in rectangular plates, m.p. 121–122° C; $[\alpha]_D^{25}$ +40.3° (*c*, 0.6, $CHCl_3$). Found: C, 79.31%; H, 9.97%; COOH, 15.23%. Calculated for $C_{20}H_{30}O_2$: C, 79.42%; H, 10.00%; COOH, 15.0%. The acid formed a cyclohexylamine salt from which the free acid could be regenerated. Treatment with diazomethane gave the crude methyl ester, m.p. 101–102° C. On recrystallization twice from methanol, the melting point was raised to 108–109° C. Found: C, 79.64%; H, 10.08%; $[\alpha]_D^{26}$ +50.5° (*c*, 2%, $CHCl_3$). Calculated for $C_{21}H_{32}O_2$: C, 79.70%; H, 10.19%. The methyl ester could not be hydrolyzed, even on prolonged treatment with potassium hydroxide in 2-methoxyethanol at 125° C. Microhydrogenation in methanol – acetic acid (4:1) with platinum oxide gave a hydrogen uptake of 3 mole equivalent. The maleic anhydride adduct of the methyl ester was prepared in the usual manner; m.p. 171° C, $[\alpha]_D$ +79.5°. Arya *et al.* (11) report for the methyl ester m.p. 105–106° C, $[\alpha]_D$ +47.0° and for the maleic anhydride adduct, m.p. 169–171° C, $[\alpha]_D$ +85°. Hydrogenation of the methyl ester in methanol over platinum oxide gave the hexahydro derivative. Found: C, 78.39%; H, 11.50%; $[\alpha]_D^{25}$ +50.75° (*c*, 1.2, $CHCl_3$). Calculated for $C_{21}H_{36}O_2$: C, 78.26%; H, 11.8%. This methyl ester could also not be saponified.

Ether-soluble Material

The resinous residue (465 g) after ligroin extraction was extracted twice with boiling ether (1 liter) and the ether was decanted from the viscous residue. The extract was filtered and concentrated (500 ml). A small aliquot was evaporated to dryness and the total yield was calculated to be 60 g. The ethereal solution was then successively extracted with 5% aqueous solution of sodium carbonate (fraction D) and sodium hydroxide (fraction E), washed with water, dried over sodium sulphate, and the solvent was distilled off (fraction F).

Fractions D and E (40.0 g)

On acidification a bright red oil was obtained which was taken up in ether. Attempts to crystallize the material failed. With alcoholic ferric chloride solution a bright green color was obtained. Paper chromatography (12) did not reveal the presence of any thujaplicins or nootkatin.

Fraction F (10.0 g)

On long standing the concentrated solution in ethanol deposited yellow prisms (0.2 g), m.p. 142–144° C. The infrared spectrum was similar to that of savinin in all respects and the mixed melting point was undepressed.

Acetone-soluble Residue (350 g)

The residue was taken up in acetone (1.5 liter) and allowed to stand in the cold for several weeks when a small quantity (10 g) of microcrystalline brown material was deposited. The filtered and dried material gave a positive ferric chloride reaction. Its infrared spectrum confirmed the phenolic character.

Extraction and Analysis of the Bark

The finely powdered bark (2.1 kg) was extracted continuously with ligroin (b.p. 60–80° C) in a Soxhlet extractor for 24 hours. The soluble material (71 g) was divided into neutral (41 g) and acidic (26 g) fraction as above.

Neutral Components

Silicic acid chromatography (see above) gave again five fractions. The first fraction (3.0 g) was composed of sesquiterpene hydrocarbons and a small amount of the esters of fraction 2. The sesquiterpenes were purified by distillation *in vacuo*. GLC analysis gave seven peaks with RRT, 0.85, 1.00, 1.19, 1.62, 1.76, 2.29, and 2.50 in 1, 63, 21, 8, 2, 1, and 3% amounts respectively. The two major peaks corresponded in retention time to α-cedrene and thujopsene. However, permanganate oxidation did not give the expected α-cedrene diol. Selenium dioxide oxidation gave a liquid aldehyde which showed a single peak with retention time equal to thujopsenal on GLC analysis.

The second fraction (20 g) was composed of fatty acid esters and was again found to yield β-sitosterol, m.p. 136–137° C, and a mixture of fatty acids on saponification. Fraction 3 (5.0 g) differed from fraction III of the neutrals of the wood. The infrared spectrum indicated esters of long-chain fatty acid. Saponification with alcoholic sodium hydroxide gave a sesquiterpene alcohol fraction (infrared, GLC) and a fatty acid mixture in which two C_{20} acids predominated. GLC analysis of the derived methyl esters showed the C_{16}, C_{18}, and C_{20} acids to be present in the ratio of 1:2.5:3. From the mixture of acids a crystalline product, m.p. 65–70° C, was obtained in small yield. GLC analysis of this material showed it to be composed mainly of arachidic acid, with palmitic and stearic acid as contaminants. The fourth fraction (3.0 g) was divided into a volatile (b.p. 140–160° C at 3 mm) and a non-volatile component. The latter (0.6 g) crystallized from

ligroin in colorless needles, m.p. 136–137° C undepressed in admixture with β-sitosterol, m.p. 137–138° C. The infrared of the volatile material showed bands in the hydroxyl and carbonyl region. GLC analysis showed a similar mixture of ketones and alcohols as was obtained from fraction III of the wood neutrals, but the retention times of all components differed from those of the latter. The last fraction (5.0 g), when taken up in a little ethanol, again deposited small amounts of yellow needles of savinin, m.p. 145–146° C after recrystallization.

Acidic Components

The acidic material was chromatographed on silicic acid, using the same solvent as described above. The major portion (15 g) was found to be communic acid (infrared, mixed melting point). The crude acid was converted to the methyl ester with diazomethane and analyzed by GLC on the silicic acid column at 230° C. Only a single peak having the retention time of methyl communate was recorded. Three small viscous fractions were also obtained from the chromatogram, none of which crystallized. The last two gave a positive color reaction for phenols with ferric chloride solution.

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THE CONSTITUTION OF A HEMICELLULOSE OF CHERRY WOOD (PRUNUS AVIUM L. VAR. BING)[1]

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The hemicellulose isolated by direct alkaline extraction of the wood has been shown to be a 4-*O*-methyl-D-glucuronoxylan. Methylation data indicate a backbone of approximately 110 D-xylopyranose units linked by β, $1 \rightarrow 4$ bonds with single units of 4-*O*-methyl-D-glucuronic acid linked by α, $1 \rightarrow 2$ bonds. The proportion of acid units to xylose is approximately 1:7. 2,3-Di-*O*-methyl-D-lyxose was isolated as an artifact.

In a recent paper (1) attention was drawn to the fact that many of the wood hemicelluloses which have been studied are those from trees of commercial importance for the purpose of pulping. The present paper is concerned with the hemicellulose of cherry wood and is complementary to our recent study on apple wood hemicellulose (1).

Cherry wood was reduced to sawdust in a Wiley mill and extracted first with hot ethanol–benzene (1:2) and then with sodium hydroxide (0.1 *N*). The hemicellulose was extracted with sodium hydroxide (1 *N*), following the method of McDonald (2), and was recovered by pouring the solution into acidified ethanol. The yield was about 22%, based on air-dry wood, and a typical preparation had $[\alpha]_D$ −28°, raised to −38° after one reprecipitation, and an ash content of 8%.

A portion of the hemicellulose was hydrolyzed with sulphuric acid and resolved by means of ion-exchange resins into a neutral and an acidic portion. The neutral portion contained mainly D-xylose characterized as the crystalline sugar together with small amounts of D-glucose and traces of rhamnose. D-Glucose was characterized as *N*-(*p*-nitrophenyl)D-glucosylamine and rhamnose by chromatography and electrophoresis. The acidic portion appeared from chromatography to be mainly one aldobiouronic acid which was characterized as the crystalline methyl 2-*O*-[methyl(2,3-di-*O*-acetyl-4-*O*-methyl-α-D-glucopyranosyl)uronate]-3,4-di-*O*-acetyl-D-xylopyranoside. The aldobiouronic acid is thus 2-*O*-(4-*O*-methyl-α-D-glucopyranosyl uronic acid)-D-xylopyranose, which is now known to occur widely (3).

A portion of the hemicellulose was methylated first by Haworth's method and then by Purdie's. Fractional precipitation with petroleum ether from chloroform showed the product to be homogeneous, as shown in Table I. Fraction 4 was cleaved with methanolic hydrogen chloride and separated into neutral and acidic components as previously described (4).

Chromatographic examination of the acidic portion showed only one component corresponding to a partially methylated aldobiouronic acid. Accordingly, this compound was esterified and reduced with lithium aluminum hydride; however, the resulting neutral disaccharide glycoside did not crystallize as anticipated (4). Acid hydrolysis gave 3-*O*-methyl-D-xylose and 2,3,4-tri-*O*-methyl-D-glucose, each characterized as their crystalline *N*-phenyl glycosylamines.

The neutral sugar glycosides were hydrolyzed with sulphuric acid and the resulting sugars separated on a column of cellulose–hydrocellulose using butanone–water (5).

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Contribution from the Department of Chemistry, University of British Columbia, Vancouver, B.C. The material in this paper was presented at the 138th American Chemical Society meeting in New York, September, 1960, and is taken from a thesis presented for the M.Sc. degree by Miss S. A. McKelvey, October, 1960.

Initially, six fractions were obtained with a recovery of 92% but three of these were mixtures and were separately rechromatographed. The final fractions obtained are shown in Tables II–V. Components 1,4 and 7 were 2,3,4-tri-*O*-methyl-D-xylose, identified chromatographically; 2,3-di-*O*-methyl-D-xylose, identified as the crystalline sugar and the crystalline *N*-phenyl glycosylamine; and a mixture of 2- and 3-*O*-methyl-D-xylose, identified by electrophoresis. Component 2 yielded only 2,3-di-*O*-methyl-D-xylose on hydrolysis and was therefore 4-*O*-(2,3-di-*O*-methyl-D-xylopyranosyl)-2,3-di-*O*-methyl-D-xylose. The high positive rotation indicated an alpha linkage and suggested that this was a reversion product (1).

Component 5 amounted to about 10% of the mixture and had $[\alpha]_D$ −36.6° (*c*, 0.85 in water). The sugar crystallized spontaneously and on recrystallization from ethyl acetate had m.p. 113–117° C. The derived *N*-phenyl glycosylamine was crystalline but difficult to purify and had m.p. 107.5–113.5° C. Complete methylation of this derivative (6) yielded a sirup which, on hydrolysis, gave a compound with R_f 0.77 (butanone–water). These results were not consistent with any D-xylose derivative. Attempted demethylation with hydrobromic acid (7) led to extensive degradation but reaction with boron trichloride (8) gave a clean product chromatographically identical with lyxose. A mixed melting point with a sample of 2,3-di-*O*-methyl-D-lyxose showed no depression, thus confirming the identification of component 5. A re-examination of the sugars produced on hydrolysis of the original polysaccharide failed to reveal the presence of any lyxose. The 2,3-di-*O*-methyl-D-lyxose was undoubtedly produced by epimerization of 2,3-di-*O*-methyl-D-xylose caused by the free base (ca. 0.3%) present in the barium carbonate used to neutralize sulphuric acid. It is of interest that an unknown dimethylpentose with the same characteristics as those described here has been isolated from the methylated "squeegee" fraction of wheat flour (9). In this instance an ion-exchange column was used for neutralization and even with careful washing such columns are known to bleed traces of alkali. It is perhaps worth noting that, in the present work and that on the wheat flour, columns of cellulose–hydrocellulose were used. Superior resolving power has been claimed for these columns (5) and it may well be that this artifact has occurred in other hydrolyzates but has escaped detection.

Component 6 obtained in trace amount was evidently a disaccharide since on hydrolysis it yielded 2,3-di-*O*-methyl-D-xylose, identified chromatographically, and 2-*O*-methyl-D-xylose, identified electrophoretically.

From the weights of the methylated sugars obtained the polysaccharide was calculated to contain 114 xylose units with 17 acid residues per macromolecule. When the ratio of sugars was analyzed by the phenol – sulphuric acid method (10) the figures were 106 and 16. Both of these calculations give a xylose to acid ratio of 7:1, which is in good agreement with that (8:1) computed from the neutralization equivalent of the methylated polysaccharide.

In view of the small amount of monomethylxylose obtained, these results suggest that cherry wood hemicellulose is a linear structure (11, 12, 13). Cherry wood hemicellulose is similar to other glucuronoxylans isolated from deciduous trees but has a higher proportion of uronic acid than sugar maple (14), white birch (15, 16), yellow birch (17), and beech (18) and more closely resembles white elm (19) and apple (1). The present investigation contributes to the study of hemicellulosic materials and, together with the parallel study on apple wood, shows that these two members of the Rosaceae family conform to the general pattern of wood hemicelluloses (3).

EXPERIMENTAL

All evaporations were carried out under reduced pressure and at a bath temperature not exceeding 40° C. Optical rotations were recorded at 22±2° C.

The descending technique was used for paper chromatography with the following solvent systems:

(A) butanone–water azeotrope (20);
(B) ethyl acetate – acetic acid – formic acid – water, 18:3:1:4 (21);
(C) pyridine – ethyl acetate – water, 1:2:2 (22);
(D) 1-butanol–ethanol–water–ammonia, 40:11:19:1 (7);
(E) *s*-collidine (23);
(F) 1-butanol saturated with water (7);
(G) 1-butanol–acetone–water, 4:5:1 (24).

The last solvent system requires that the paper be impregnated with phosphate buffer solution (pH 5). Whatman No. 1 paper was used for all chromatograms except where specified, and sugars were detected with either *p*-anisidine trichloroacetate (7) or aniline phosphate (25).

Paper electrophoresis was carried out with 0.05 *M* sodium borate solution on Whatman No. 1 paper at a voltage of 1000±50 v.

Extraction of Hemicellulose

Cherry wood sawdust (424 g) was extracted for 8 hours with hot ethanol–benzene (1:2). The sawdust was air-dried and then extracted at room temperature with sodium hydroxide (0.1 *N*, 8.8 ml/g of sawdust) for 48 hours and the highly colored solution discarded. The residue was washed with water and air-dried and re-extracted with sodium hydroxide (1 *N*, 8.6 ml/g) for 48 hours at room temperature. The alkaline solution was filtered and the residue washed with water. The hemicellulose was precipitated by pouring the solution into ethanol acidified with acetic acid. The yield (determined on an aliquot) was 22% of the air-dried wood. The hemicellulose had $[\alpha]_D$ −28° (*c*, 1 in 8% NaOH) raised to $[\alpha]_D$ −38° after one reprecipitation. Ash content was 7.8%.

Hydrolysis of the Hemicellulose

Hemicellulose (30 g) was hydrolyzed with *N* sulphuric acid (1 liter) on the steam bath for 16 hours. The residue (4.8 g) was removed by filtration and the filtrate neutralized with barium carbonate. The filtrate was passed through Amberlite IR-120 and Duolite A-4 and the eluate containing the neutral sugars evaporated to a sirup (24.4 g). The acidic components were eluted from the anion exchange resin with sodium hydroxide (1 *N*, 75 ml) and the solution deionized by passage through fresh Amberlite IR-120. Concentration of the acidic eluate gave a sirup (2.2 g).

Identification of Neutral Sugars

Paper chromatography of the neutral sirup in solvents A, B, D, F, and G showed predominantly xylose with small amounts of glucose and rhamnose. When the sirup was dissolved in ethanol the D-xylose crystallized and after recrystallization from ethanol had m.p. and mixed m.p. 146–147.5° C, $[\alpha]_D$ 17.7° (*c*, 0.78 in water).

The mother liquor from the initial crystallization of the D-xylose was streaked on 10 sheets of Whatman No. 3MM (6 in.×22 in.) and the sheets developed in solvent B for 20 hours. The area corresponding to glucose was eluted with three 100-ml portions of water. Evaporation gave a sirup (80 mg), $[\alpha]$ 36° (*c*, 1.6 in water), which was chromatographically identical with D-glucose in solvent C. The extracted sugar (60 mg) and

p-nitroaniline (61 mg) were dissolved in methanol (2 ml) containing one drop of concentrated hydrochloric acid and the solution heated on the steam bath for 5 minutes. On evaporation of part of the solvent the *N*-(*p*-nitrophenyl) D-glucosylamine crystallized and on recrystallization from methanol had m.p. 173–175.5° C (26). A standard derivative had m.p. 174.5–176.5° C and a mixed melting point gave 173–176° C. The corresponding derivative (m.p. 205–207.5° C) was prepared from D-galactose for comparison. The trace of rhamnose was not separated but was identified by chromatography (R_f 0.33 in solvent G) and by electrophoresis (M_g 0.47).

Identification of the Aldobiouronic Acid

Chromatographic examination of the acidic fraction in solvent B indicated that it was essentially an aldobiouronic acid (R_{xylose} 0.97) together with some free uronic acid (R_x 1.13) and a trace of material with R_x 0.72. The acidic portion was streaked on Whatman No. 1 and developed in solvent B for 16 hours. Elution of the aldobiouronic acid (R_x 0.97) gave a sirup (323 mg) which was dissolved in methanol (28 ml) to which was added methanolic hydrogen chloride (5%, 26 ml). The solution was refluxed for 10 hours and the ester glycoside recovered as a sirup (307 mg), which was acetylated. The yield of methyl 2-*O*-[methyl (2,3-di-*O*-acetyl-4-*O*-methyl-α-D-glucopyranosyl) uronate]-3,4-di-*O*-acetyl-D-xylopyranoside was 75 mg with m.p. and mixed m.p. 193–195° C (27).

Methylation of the Hemicellulose

Hemicellulose (22 g) was dissolved in sodium hydroxide solution (8%, 100 ml) and solid sodium hydroxide (31.4 g) added. The polysaccharide was methylated at 50° C by the dropwise addition of dimethyl sulphate (300 ml) and sodium hydroxide (30%, 900 ml) over one and a half hours with the periodic addition of acetone to control foaming. When the flask was heated in a boiling water bath to decompose excess methyl sulphate the partially methylated material separated as a curd on the top of the solution and was readily filtered off. The curd, which contained much inorganic matter, was repeatedly extracted with boiling methanol and evaporation of the solvent after filtration gave the partly methylated polysaccharide (20.9 g). This material was methylated with Purdie's reagents, initially using methanol as a solvent (twice), then acetone, and finally only methyl iodide. The material thus obtained (10.3 g) was dissolved in chloroform (100 ml) diluted with diethyl ether (100 ml) and fractionally precipitated by the addition of petroleum ether to a mechanically stirred solution. The results are shown in Table I. Fractions 1 and 2 contained inorganic matter and were discarded. Fractions

TABLE I

Fractional precipitation of methylated cherry wood hemicellulose

Fraction	Total petroleum ether added, ml	Weight, g	$[\alpha]_D^{25}$ ($CHCl_3$)	Methoxyl, %
1	150	—	—	—
2	170	—	—	—
3	200	1.02	−60.0°	39.2
4	275	2.27	−60.0°	39.1
5	350	2.01	−47.1°	38.2
6	450	0.37	—	—
7	550	0.19	—	—
8	—	1.17	—	—

3–5, which initially precipitated as oils, were separately redissolved in chloroform (15 ml) and precipitated as white flocculent solids by pouring the solution into petroleum

ether (200 ml). Infrared analysis of these fractions showed the absence of a hydroxyl band. Fractions 6 and 7 could be obtained only as oils and fraction 8 was obtained by evaporating the mother liquor from fraction 7 to dryness.

The neutralization equivalent was determined by dissolving a portion of the methylated hemicellulose (211 mg, fraction 3) in potassium hydroxide (0.0810 *N*, 5.00 ml) and back titrating with sulphuric acid (0.1000 *N*) after 4 hours using a pH meter. The titer was 2.65 ml corresponding to an equivalent weight of 1510. Other samples gave 1665 and 1490.

Methanolysis and Hydrolysis of the Methylated Hemicellulose

Fraction 4 (2.27 g) was dissolved in methanolic hydrogen chloride (3%, 50 ml) and the solution refluxed on the steam bath for 7 hours when the optical rotation was constant, $[\alpha]_D$ 70°. The solution was neutralized with lead carbonate, centrifuged, and evaporated to a thick sirup of the methyl glycosides (2.25 g). The methyl esters were saponified with barium hydroxide, volatile highly methylated glycosides were extracted with petroleum ether, and the mixture separated on ion-exchange columns into acidic components (0.478 g) and neutral components (1.69 g) as previously described (4).

Identification of the Acidic Portion

The acidic component (478 mg) was dissolved in methanol (25 ml) and treated with an excess of ethereal diazomethane. The ester (339 mg) was dissolved in tetrahydrofuran (12 ml) and a solution of lithium aluminum hydride (0.5 g) in dry tetrahydrofuran (20 ml) added. The reaction was completed by refluxing for 1 hour when excess hydride was decomposed by the addition of an ethereal solution of ethyl acetate. The reduced material was acetylated without isolation and the acetate (367 mg) deacetylated with aqueous methanolic sodium hydroxide to give the neutral disaccharide glycoside (229 mg) as previously described (4). Since the disaccharide did not crystallize, even on seeding, it was identified as follows. The disaccharide (221 mg) was dissolved in methanolic hydrogen chloride (3%, 10 ml) and refluxed for 5 hours. After neutralization (Ag_2CO_3), treatment with hydrogen sulphide, filtration, and evaporation, there was obtained a clear sirup (208 mg) which was dissolved in sulphuric acid (1 *N*, 5 ml) and heated on the steam bath for 6 hours. The solution was neutralized by passage through Duolite A-4, and concentration of the effluent gave a sirup (215 mg) which was separated on a cellulose–hydrocellulose column using butanone–water and a collecting time of 20 minutes (5). The faster-migrating component (tubes 9–21, 75 mg) was chromatographically identical with 2,3,4-tri-*O*-methyl-D-glucose and had $[\alpha]_D$ 81.6° (*c*, 1.5 in water). Literature (28) $[\alpha]_D$ 86°. The 2,3,4-tri-*O*-methyl-*N*-phenyl-D-glucosylamine was recrystallized from ethyl acetate – petroleum ether and had m.p. 141–143° C undepressed by an authentic sample (29).

The contents of tubes 60–78 gave a colorless sirup (39 mg) electrophoretically identical with 3-*O*-methyl-D-xylose and having $[\alpha]_D$ 22.3° (*c*, 0.78 in water). Literature (30) $[\alpha]_D$ 17°. The 3-*O*-methyl-*N*-phenyl-D-xylosylamine was recrystallized from ethyl acetate – petroleum ether, m.p. 130–131° C.

Identification of the Neutral Sugars

The neutral glycosides (1.69 g) were dissolved in sulphuric acid (1 *N*, 60 ml) and heated on the steam bath for 8 hours. After neutralization ($BaCO_3$) and evaporation, there was obtained a sirup (1.57 g), part of which (1.24 g) was dissolved in butanone–water (2 ml); a few drops of Sudan IV dye were added. The solution was added to the

top of a column (40×3 cm) packed with a 1:1 mixture of cellulose and hydrocellulose (5). Solvent A was used for elution and the effluent was collected at 10-minute intervals

TABLE II

First separation of neutral sugars of hemicellulose on a hydrocellulose–cellulose column

Fraction	Tube number	Component number	Weight, mg
A	10	1	3
B	11–30	1, 2, 3, 4	206
C	31–40	4	505
D	41–64	4, 5	228
E	65–98	5, 6	128
F	119–135	7	23
			Recovery 92.3%

for 117 tubes and then at 30-minute intervals for 18 tubes. Fractions A–F were obtained with a 92% recovery but, of these, B, D, and E contained mixtures and were separately passed through the column again. Pooling the tubes which, by paper chromatography, had been shown to contain similar materials resulted in establishing the presence of eight sugars. The details of these separations are shown in Tables III–V.

TABLE III

Reseparation of fraction B of neutral sugars of hemicellulose

Tube number	Component number	Weight, mg	Identity of component
20–21	1	—	2,3,4-Tri-*O*-methyl-D-xylose
22–29	1, 2	11	
30	2	—	Disaccharide A
31–39	2, 3	4	
40–51	3	11	Unknown A
54–59	4	8	2,3-Di-*O*-methyl-D-xylose
60–80	4	—[a]	2,3-Di-*O*-methyl-D-xylose

[a]This material was combined with tubes (30–40) of reseparation of fraction D.

TABLE IV

Reseparation of fraction D of neutral sugars of hemicellulose

Tube number	Component number	Weight, mg	Identity of component
30–40	4	199	2,3-Di-*O*-methyl-D-xylose
41–47	4, 5	10	
48–65	5	92	2,3-Di-*O*-methyl-D-lyxose

TABLE V

Reseparation of fraction E of neutral sugars of hemicellulose

Tube number	Component number	Weight, mg	Identity of component
31–45	4	4	2,3-Di-*O*-methyl-D-xylose
52–68	5	—[a]	2,3-Di-*O*-methyl-D-xylose
69–73	5, 6	2	
74–100	6	9	Disaccharide B

[a]This material was combined with tubes (48–65) of reseparation of fraction D.

Component 1.—Chromatographically identical with 2,3,4-tri-*O*-methyl-D-xylose.

Component 2.—Acidic hydrolysis of the contents of tube 30 from the reseparation of fraction B gave only 2,3-di-*O*-methyl-D-xylose. Since the specific rotation of tubes 22–29 was 77.5° (*c*, 0.64 in water) component 2 was assumed to be 4-*O*-(2,3-di-*O*-methyl-α-D-xylopyranosyl)-2,3-di-*O*-methyl-D-xylose.

Component 3.—Acid hydrolysis gave no change. It gave an unusual green color with aniline phosphate spray and was chromatographically unlike 2,3,4,6-tetra-*O*-methyl-D-galactose.

Component 4.—The sirup crystallized spontaneously and after recrystallization from ethyl acetate – petroleum ether had m.p. 98–101° C and $[\alpha]_D$ 21.4° (*c*, 0.58 in water). The mixed melting point was undepressed with an authentic sample of 2,3-di-*O*-methyl-D-xylose with m.p. 95–100° C. The derived 2,3-di-*O*-methyl-*N*-phenyl-D-xylosylamine had m.p. 121–123° C. Literature (31) m.p. 120–122° C.

Component 5.—This was unchanged by acid hydrolysis and did not migrate on electrophoresis. The sirup crystallized spontaneously and on recrystallization from ethyl acetate had m.p. 113–117° C, $[\alpha]_D$ −36.6° (*c*, 0.85 in water). OMe, calculated for a dimethylpentose 34.8%. Found, OMe 34.5%. The reported constants for 2,3-di-*O*-methyl-D-lyxose are m.p. 116–117° C, $[\alpha]_D$ −10.7° (*c*, 0.3 in water) and a mixed melting point of an authentic sample of this compound with component 5 gave no depression (32).

The derived 2,3-di-*O*-methyl-*N*-phenyl-D-lyxosamine had m.p. 107.5–113.5° C. Literature (32) 107–108° C. When this compound (50 mg) was methylated with methyl iodide (10 ml) and silver oxide (200 mg) the recovered fully methylated anilide (41 mg) did not crystallize (9). Hydrolysis of a small portion (33) and chromatographic analysis in solvent A gave a compound with R_f 0.77.

Two attempts to demethylate component 5 using hydrobromic acid (7) led to extensive degradation. Demethylation using the boron trichloride procedure (8) gave a clean product which was readily shown to be identical with lyxose both by chromatography in solvent G (R_f 0.25) and by electrophoresis (M_g 0.83).

Component 6.—This was evidently a disaccharide since hydrolysis of the contents of tube 74 from the reseparation of fraction E gave 2,3-di-*O*-methyl-D-xylose and a monomethylxylose (by chromatography). The latter was shown by electrophoresis to be 2-*O*-methyl-D-xylose (M_g 0.37).

Component 7.—Electrophoresis showed this to be a mixture of 2- and 3-*O*-methyl-D-xylose in which the former predominated.

Qualitative Analysis

The composition of the contents of tubes containing two components was computed from optical rotations and these weights added to the weight of the appropriate pure component previously isolated. Making allowances for the mechanical losses involved in the reseparations the weights of sugars obtained were in the ratio of 2:94:1:17 for mono-, di-, and tri-*O*-methylpentose and aldobiouronic acid respectively.

Standard curves were prepared for the phenol – sulphuric acid method (10) using 2-*O*-methyl-D-xylose, 2,3-di-*O*-methyl-D-xylose, and 2,3,4-tri-*O*-methyl-D-xylose. Each sugar gave a linear plot over the range 0–35 micrograms/ml and the curves for the mono- and di-*O*-methyl-D-xyloses were virtually identical with an O.D. 0.275 for 35 microgram/ml. The tri-*O*-methyl-D-xylose gave an O.D. of 0.40 for 20 microgram/ml. A portion of the neutral methylated sugars was streaked on a sheet of Whatman No. 1 (6 in. × 22 in.) and developed in butanone–water. Appropriate sections of the paper were

eluted each with 20 ml of water. These solutions had to be diluted 1:1, 1:100, and 1:3 for the estimation of the tri-, di-, and mono-methylpentoses and the results gave a molar ratio of 1:88:1, respectively.

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THE ELECTRONIC ABSORPTION SPECTRA OF DIXANTHOGENS[1]

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ABSTRACT

The electronic absorption spectra of diethyl, diisopropyl, di-*n*-butyl, and diisoamyl dixanthogens have been studied in polar and non-polar solvents. The compounds exhibit a low-intensity band around 365 mμ and two high-intensity bands around 285 and 242 mμ. The 365 mμ band is assigned, as a result of the solvent studies, to $n \rightarrow \pi^*$ transition and the 285 mμ band to $\pi \rightarrow \pi^*$ transition. The band around 242 mμ may be due to the $n \rightarrow \sigma^*$ transition, since in polar solvents it shows mainly a blue shift.

The available data on the electronic absorption spectra of organic sulphur compounds having thiocarbonyl group are relatively meager in the literature (1, 2). Janssen (2) has reviewed the previous work on sulphur compounds and studied the nitrogen-containing thiones extensively. Recently, the present authors studied the infrared spectra of dixanthogen compounds (3). In this paper, studies on the near-ultraviolet spectra and solvent effect on the various bands exhibited by dixanthogens are described.

EXPERIMENTAL

Diethyl, diisopropyl, di-*n*-butyl, and diisoamyl dixanthogens were prepared, purified, and analyzed as described in an earlier paper (4). The electronic absorption spectra of these compounds were studied in heptane, cyclohexane, ethanol, and acetonitrile solutions on a Hilger spectrophotometer, Model H 700, using 1-cm quartz matched cells. Since these compounds are non-ionogenic, their spectra could not be studied either in an acid or in water medium. The solvents employed were purified by the methods recommended by Weisberger and Proskauer (5). The wavelengths of absorption maxima are recorded in millimicrons and the molar extinction coefficients are expressed in terms of log ϵ.

RESULTS AND DISCUSSION

The peak wavelengths and molar extinction coefficients of ultraviolet absorption maxima for dixanthogens in various solvents are given in Table I. Typical absorption

TABLE I

Peak wavelengths and molar extinction coefficients for dixanthogens in different solvents

	Hydrocarbon		Ethanol		Acetonitrile	
Compound	λ_{max}	log ϵ	λ_{max}	log ϵ	λ_{max}	log ϵ
Diethyl dixanthogen	240	4.34	239	4.32	239	4.34
	279	3.91	281	3.90	283	3.91
	363	1.90	361	1.91	360	1.93
Diisopropyl dixanthogen	243	4.36	241	4.35	240	4.30
	285	3.92	286	3.94	287	3.91
	365	1.91	362	1.90	360	1.92
Di-*n*-butyl dixanthogen	244	4.38	243	4.37	243	4.38
	286	3.92	287	3.91	288	3.90
	365	1.91	362	1.92	360	1.92
Diisoamyl dixanthogen	245	4.39	243	4.38	242	4.38
	286	3.95	287	3.92	288	3.97
	367	1.92	363	1.91	360	1.91

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curves of diisoamyl dixanthogen in cyclohexane and acetonitrile are given in Fig. 1.

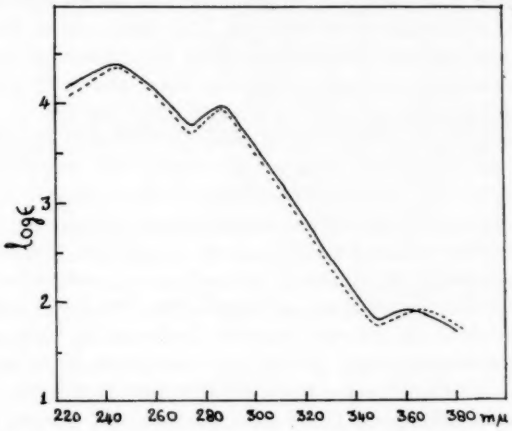

FIG. 1. Ultraviolet absorption spectra of diisoamyl dixanthogen in cyclohexane (- - -) and in acetonitrile (——).

Inspection of the results in Table I shows that all the dixanthogens give three absorption bands. The first low-intensity band is noticed around 365 mμ (log ε 1.9) and two high-intensity bands are observed around 285 mμ (log ε 3.9) and 242 mμ (log ε 4.4.). The molar extinction coefficients (log ε 1.9) for the low-intensity band around 365 mμ compare well with the values given by Treiber (6) and Lowry and Hudson (7) for other dixanthogens. It is well known that the molecules which contain the thiocarbonyl group have a low-intensity absorption band at a longer wavelength similar to the 365 mμ band obtained for the dixanthogens. This band is found to show a blue shift on changing the solvent from a non-polar to a polar solvent. Further, with the increase in the polarity of the solvent, the band shows increased blue shift. This shows that the transition energy involved increases with the increase in the polarity of the solvent. According to an empirical rule (8, 9), this band can be characterized by $n \rightarrow \pi^*$ transition. This absorption is accounted for by the excitation of an electron from the non-bonding lone pair of electrons (n orbital) localized on the double-bonded sulphur into an antibonding π orbital (π^*). Mulliken (10) has pointed out that the thiocarbonyl group has an electronic structure similar to that of the carbonyl group and that the thiocarbonyl absorption regions are expected at wavelengths longer than that of the carbonyl group because the $3p_y$ electron of the sulphur is less firmly bound than that of the $2p_y$ electron of the oxygen. The origin of the $n \rightarrow \pi^*$ blue shift may be attributed to solvation (11) and(or) hydrogen bonding (12) between the non-bonding electrons of the thiocarbonyl group of the solute and the solvent molecules. The $n \rightarrow \pi^*$ blue shift observed, when the solvent was changed from a non-polar to a polar non-hydrogen-bonding (13) acetonitrile, could be explained by the formation of an electrostatic bond between the non-bonding electrons of the thiocarbonyl sulphur atom and the positively charged carbon atom of the nitrile group. Such a bond lowers the energy of the n-electron orbital, and upon excitation, the electrostatic bond is either broken or weakened. A similar explanation has been advanced by Becker (14) to explain the blue shift in the acetonitrile solvent for the $n \rightarrow \pi^*$ band of carbonyl group of benzophenone.

The intense band around 285 mμ (log ε 3.9) shows a red shift when the solvent is changed from a non-polar to a polar one. A small increase in red shift is observed with the increase in the polar character of the solvents. This band can be ascribed to $\pi \rightarrow \pi^*$ transition (8, 9), where an electron jump occurs from the highest occupied π orbital to the lowest empty (antibonding) π level. A similar band observed around 278 mμ in *s*-ethyl *o*-ethyl xanthate has been assigned as $\pi \rightarrow \pi^*$ transition (2).

The intense band around 242 mμ (log ε 4.4) in dixanthogens is analogous to the 220–250 mμ band exhibited in *s*-ethyl *o*-ethyl xanthate (15), alkali metal xanthates (16), and also in dialkyl disulphides (17). This band in dixanthogens shows mainly a blue shift when the solvent is changed from a hydrocarbon to ethanol and acetonitrile. This band may, therefore, be characterized by $n \rightarrow \sigma^*$ transition. It is expected that the solvent effect on the $n \rightarrow \sigma^*$ transition should be similar to that of the $n \rightarrow \pi^*$ transition but little is known about the solvent effect on this type of transition. The $n \rightarrow \sigma^*$ transition can be explained by the excitation of an electron from the non-bonding lone pair of electrons, localized on the σ-bonded sulphur atoms in the —*s*—*s*— group, to an antibonding level, either 3*d* or 4*s*. This $n \rightarrow \sigma^*$ band assignment finds support from the 225 mμ band of *s*-ethyl *o*-ethyl xanthate, in which case Janssen (2) observed a blue shift to below 215 mμ when concentrated sulphuric acid was used as a solvent.

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THE PREPARATION OF ERYTHRO-3-PENTULOSE[1]

R. J. STOODLEY

ABSTRACT

The mercuric acetate oxidation of ribitol yielded a mixture of *erythro*-3-pentulose and DL-erythro-2-pentulose.

INTRODUCTION

The hydroxyl groups of alditols may be oxidized by a variety of chemical procedures. The oxidants may be relatively non-specific, oxidizing both primary and secondary hydroxyl groups, or they may be specific. Non-specific oxidizing agents include Fenton's reagent (1), the halogens (2), and oxygen in the presence of platinum (3). Generally the yield of aldoses and ketoses is low. Nitrogen dioxide (4) and, in some cases, oxygen in the presence of a platinum–carbon catalyst (5) are examples of specific oxidants which oxidize primary alcohol groups to carboxyl groups in reasonable yield. Chromium trioxide has been found to be a valuable reagent for oxidizing secondary alcohol groups to keto groups in alditols, providing all the other hydroxyl groups are suitably blocked (6).

There appears to be no chemical procedure for selectively oxidizing secondary alcohol groups in the presence of unsubstituted primary hydroxyl groups. In some cases, however, this oxidation may be achieved biochemically using *Acetobacter suboxydans*. In fact this organism has been used to prepare 1-deoxy-D-*xylo*-3-hexulose from L-fucitol (7), the preparation being the first recorded for a 3-ketose.

The first chemical synthesis of a 3-ketose was achieved by Jones (8), who prepared 2-*O*-methyl-L-*xylo*-3-hexulose from L-ascorbic acid. In attempting to synthesize an unsubstituted 3-ketose, Sugihara and Yuen (9) prepared crystalline 4-*O*-benzoyl-1,2:5,6-di-*O*-isopropylidene-D-*arabo*-3-hexulose by the chromium trioxide oxidation of 3-*O*-benzoyl-1,2:5,6-di-*O*-isopropylidene-D-mannitol. However, attempts to remove the protecting groups resulted in the formation of a mixture of ketose sugars, presumably because debenzoylation proceeded via an enediol intermediate. Starting with 6-*O*-benzoyl-1,2:4,5-di-*O*-isopropylidene-DL-galactitol, the same authors have recently obtained crystalline DL-*xylo*-3-hexulose (10), realizing the first chemical synthesis of an unsubstituted 3-hexulose.

Schaffer has reported the preparation of D-*manno*-3-heptulose by the lead tetraacetate oxidation of 3-*C*-formyl-D-*glycero*-D-*talo*heptitol (11), and has recently crystallized the material (12).

The isolation of *erythro*-3-pentulose from the mercuric acetate oxidation of ribitol represents the first chemical synthesis of a 3-pentulose. DL-*erythro*-2-Pentulose was also produced, but the failure to detect ribose (or any product obtained by the mercuric acetate oxidation of D-ribose) suggests that the oxidant may be specific for secondary hydroxyl groups.

erythro-3-Pentulose may be an important biological intermediate. D-*erythro*-2-Pentulose 1,5-diphosphate has been shown to be the prime acceptor of carbon dioxide in photosynthesis, and Wilson and Calvin (13) have suggested that its dismutation to phosphoglyceric acid may involve the 3-ketose intermediate. Ashwell and Hickman (14) incubated D-ribose 5-phosphate with a mouse spleen extract and, after dephosphorylating

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Contribution from the Department of Chemistry, Queen's University, Kingston, Ontario.

the products, they isolated D-*threo*-2-pentulose and D-*erythro*-2-pentulose and small amounts of a third material which they tentatively characterized as *erythro*-3-pentulose. They suggested that the phosphorylated 3-ketose was an intermediate in the interconversion of D-*erythro*-2-pentulose 5-phosphate and D-*threo*-2-pentulose 5-phosphate. A similar intermediate was also detected by Dickens and Williamson while they were studying the same reaction using a rabbit muscle enzyme preparation (15).

DISCUSSION

Ribitol was oxidized with mercuric acetate in methanol at 38° C. Removal of the mercury salts after 4 weeks led to the 70% recovery of a syrup which was shown by paper chromatography to contain ribitol and two reducing sugars, distinct from ribose. Part of the ribitol was removed by crystallization and the remaining material was fractionated on an ion-exchange column (16); 50% of the ribitol was recovered in crystalline form.

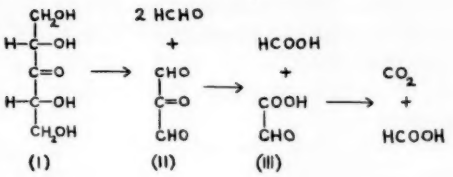
The faster-moving reducing sugar was obtained in about 18% yield (based on the amount of ribitol oxidized) and was further purified by paper chromatography. The material rapidly reduced Fehling's solution at room temperature and gave a brown coloration with *p*-anisidine. In contrast to the results of Dickens and Williamson (15), the ketose did not give a positive reaction with orcinol – trichloroacetic acid (17) nor when oversprayed (18) with aniline phosphate (19) in the cold. An aqueous solution of the 3-ketose did not react in the cysteine–carbazole assay (20) nor in the supposedly specific 3-pentulose test with cysteine and sulphuric acid developed by Ashwell (21). These results show that the synthetic material is different from the ketose isolated from biological systems.

The sugar was reduced with sodium borohydride and crystalline ribitol was isolated. Examination of the acetylated, reduced syrup by gas–liquid partition chromatography using the procedure of Gunner *et al.* (22) showed the presence of ribitol and xylitol pentaacetates, thus establishing the presence of a keto group at carbon atom 3.

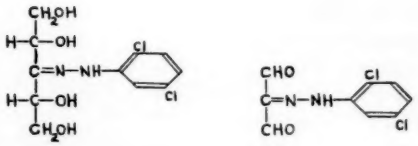
Oxidation of the pentulose with sodium metaperiodate under unbuffered conditions resulted in the rapid liberation of 1.8 moles of formaldehyde. This result demonstrated the presence of two primary alcohol groups in the molecule and left little doubt that the sugar was *erythro*-3-pentulose (I). The consumption of 4.06 moles of periodate and production of 2.05 moles of titratable acid further substantiated this structure. The results indicate that (I) is rapidly cleaved to 2 moles of formaldehyde and mesoxalaldehyde (II), and that the latter molecule is immediately oxidized to formic acid and glyoxylic acid (III). The slower uptake of the fourth mole of periodate (ca. 90 minutes) is consistent with the known rate of oxidation of glyoxylic acid (III) to carbon dioxide and formic acid under unbuffered conditions (23).

The periodate oxidation studies and the presence of a carbonyl absorption in the ultraviolet region (ϵ_{max} 70 at 280 mμ) suggest that the 3-pentulose is in the acyclic form (I) in aqueous solution. However, the ready enolization of the syrup to a mixture of *threo*- and *erythro*-2-pentuloses (which presumably exist as furanose rings) demonstrates the lability of the acyclic structure in the syrupy state.

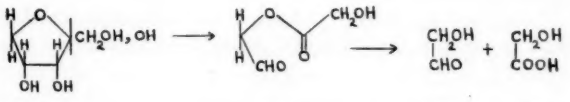
The pentulose formed a crystalline 2,5-dichlorophenylhydrazone. That enolization did not occur during this reaction was shown by the regeneration of the original pentulose and by periodate oxidation studies. The 2,5-dichlorophenylhydrazone (IV) consumed 2.20 moles of periodate and liberated 0.19 mole of titratable acid and 1.8 moles of formaldehyde. A material presumed to be mesoxalaldehyde-2-(2,5-dichlorophenylhydrazone)



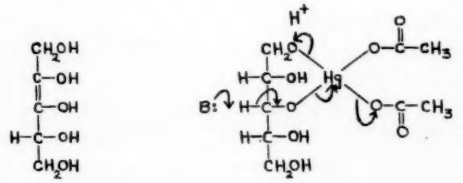
(I) (II) (III)



(IV) (V)



(VI) (VII) (VIII) (IX)



(X) (XI)

(V) was also obtained. The small uptake of periodate (0.2 mole) and production of formic acid (0.19 mole) in excess of the expected values suggest that (V) is attacked by periodate.

The chemical evidence strongly indicates that the sugar is *erythro*-3-pentulose. It is possible that the material isolated by Ashwell and Hickman and subsequent workers may be D-*glycero*-2,3-pentulose.

The slower-moving reducing sugar was the last component to be eluted from the column and was obtained in about 11% yield (based upon the amount of ribitol oxidized). The product was chromatographically indistinguishable from authentic *erythro*-2-pentulose and contained no *threo*-2-pentulose when examined by paper electrophoresis. The material was estimated by the cysteine–carbazole reaction (20) and characteristic peaks were produced at 540 and 390 mμ. The absorption was measured after 15 minutes and did not change within 2 hours. An authentic specimen of *threo*-2-pentulose increased in absorption during this interval (24).

The pentulose consumed 2.06 moles of periodate and liberated 1.01 moles of formic acid and 0.19 mole of formaldehyde when oxidized under unbuffered conditions for 6 hours. An additional mole of periodate was taken up when the oxidation was performed in phosphate buffer at pH 8 and the formaldehyde liberated increased to 0.93 mole. These results are consistent with the oxidation of *erythro*-2-pentulose in the furanose

form (VI) rather than the acyclic form. Presumably the glycolic acid ester of glycolaldehyde (VII) is first formed and is stable under unbuffered conditions, but is hydrolyzed to glycolic acid (IX) and glycolaldehyde (VIII) at pH 8. Glycolic acid (VIII) is known to be stable to periodate (25) while glycolaldehyde (IX) rapidly consumes 1 mole to give formaldehyde and formic acid.

Although there is little information about the mechanism of the oxidation, the ratio of *erythro*-3-pentulose to *erythro*-2-pentulose isolated (approximately 2:1) indicates that the hydroxyl group at carbon atom 3 is more readily oxidized than that at carbon 2 (unless *erythro*-2-pentulose is further oxidized). It seems unlikely that the enediol (X) is an intermediate since *threo*-2-pentulose was not detected in the reaction mixture. If formed, the enediol would be expected to enolize in the direction of the 2-pentuloses (which are presumably stabilized by internal hemiketal formation), especially as the isolated 3-pentulose enolized in this manner.

It is possible to explain the results by predicting the intermediate formation of six-membered rings containing mercury. DL-*erythro*-2-Pentulose may be produced by oxidation of the cyclic intermediate involving the oxygen atoms attached to carbon atoms 2 and 4. The failure to detect ribose (or methyl ribonate) may indicate that the cyclic intermediate involving the primary alcohol is cleaved to *erythro*-3-pentulose as is suggested in (XI).

EXPERIMENTAL

Melting points were determined on a Kofler hot stage and were uncorrected. Solutions were concentrated under reduced pressure at 30–40° C. Paper chromatography was carried out by the descending method on Whatman No. 1 filter paper using the following solvent systems (v/v): (*a*) butan-1-ol, ethanol, water (3:1:1); (*b*) ethyl acetate, acetic acid, formic acid, water (18:3:1:4); and (*c*) butan-1-ol, pyridine, water (10:3:3). Sugars were located on chromatograms by the *p*-anisidine hydrochloride (26) or the alkaline silver nitrate (27) sprays, and their rate of movement is quoted relative to that of D-ribose (R_{rib}). Paper electrophoresis was performed using Whatman 3 MM filter paper impregnated with 0.05 *M* borate buffer (pH 9.2). Sugars were detected on paper electrophoretograms by the periodate–*p*-anisidine spray (28). Infrared spectra were determined on powdered materials dispersed in potassium bromide pellets, using a Perkin–Elmer Model 21 spectrophotometer.

Mercuric Acetate Oxidation of Ribitol (Method A)

Mercuric acetate (42.0 g) was dissolved in hot methanol (250 ml) containing 1% acetic acid. Ribitol (10.0 g) was added to the cooled solution, which was stored in an incubator at 38° C. The mercurous acetate which precipitated was removed by filtration from time to time. After 4 weeks 21.5 g of mercurous acetate was obtained and chromatographic examination of the solution in solvent *b* revealed the presence of two reducing components in addition to unreacted ribitol.

The solution was saturated with hydrogen sulphide and filtered, and the filtrate was concentrated to a syrup (7.03 g) which was dissolved in ethanol and seeded with ribitol. The crystalline material (3.10 g) was collected by filtration and cautiously washed with ethanol; m.p. 100–101° C, undepressed on admixture with authentic ribitol. The filtrate was evaporated to a brown syrup.

Fractionation of the Reaction Mixture

The syrup was fractionated in portions (ca. 1.0 g) on a column of Dowex 50 W X8 (200–400 mesh, Ba^{++}) by the method of Jones and Wall (16). The column (70×2.2 cm)

was eluted with water and fractions (ca. 3 ml) were collected automatically every 15 minutes. The result of a typical separation is shown in Table I.

TABLE I

Fractionation of sugars

Tube No.	Fraction No.	Suspected component	Weight, g
60–85	1	Ribitol	0.48
86–98	2	Ribitol + *erythro*-3-pentulose	0.05
99–125	3	*erythro*-3-Pentulose	0.23
126–190	4	DL-*erythro*-2-Pentulose	0.14

Characterization of Fraction 1 as Ribitol

The syrup (1.90 g) crystallized on standing. After recrystallization from ethanol, the material melted at 101–102° C, undepressed on admixture with authentic ribitol.

Characterization of Fraction 3 as erythro-3-Pentulose

The fraction was obtained as a pale yellow syrup (0.91 g). Chromatographic examination of the material in solvents *a*, *b*, and *c* showed that it was mainly a single component (R_{rib} 1.23 in solvent *c*), although small amounts of slower-moving materials were also detected. A portion of the syrup was refractionated on Whatman 3 MM paper using solvent *b*. End strips of the chromatogram were sprayed with *p*-anisidine and the requisite area of paper was eluted with water. The solution was lyophilized and the pale yellow syrup obtained was found to be homogeneous when examined in solvents *a*, *b*, and *c*. The material did not give a color with orcinol – trichloroacetic acid (17) nor when oversprayed (18) in the cold with aniline phosphate (19), although, when heated, it developed an orange color. A brown spot was obtained when the sugar was sprayed with *p*-anisidine. The sugar did not react to any significant extent in the cysteine–carbazole assay (20).

When stored in a vacuum desiccator containing silica gel, the syrup slowly darkened and, after 3 weeks, considerable amounts of *erythro*-2-pentulose and *threo*-2-pentulose were detected by paper electrophoresis. The properties of the 3-ketose were therefore determined on a freshly fractionated sample (26.1 mg) which was dissolved in water in a standard flask (25 ml). The solution was stored at 0° C and little enolization of the 3-ketose occurred within 3 weeks.

A solution of *erythro*-3-pentulose rapidly reduced Fehling's solution at room temperature.

Periodate Oxidation of erythro-3-Pentulose

An aliquot of the 3-ketose solution (5 ml equivalent to 5.2 mg of ketose) was added to 0.3 *M* sodium metaperiodate solution (1 ml) and the volume was adjusted to 25 ml with water. A blank was prepared by diluting sodium metaperiodate solution (1 ml) to 25 ml with water. The solutions were stored in the dark at room temperature. Samples (1 ml) were removed at intervals for the determination of the periodate uptake (29) and formic acid production (30). Formaldehyde was determined on aliquots which were diluted fivefold prior to the estimation (31). The results are recorded in Table II.

Ultraviolet Absorption of erythro-3-Pentulose

The ultraviolet absorption of a solution of *erythro*-3-pentulose in water (1.04 mg/ml) was determined with a Beckman Model DK spectrophotometer using 1-cm cells. The spectrum, which is typical of a carbonyl absorption, is shown in Fig. 1.

TABLE II

Periodate oxidation of *erythro*-3 pentulose

Time (hour)	Periodate uptake (moles/mole)	Formic acid production (moles/mole)	Formaldehyde production (moles/mole)
0.15	3.01	1.31	1.82
0.55	3.51	1.99	1.75
1.50	3.88	2.06	—
3.50	4.03	2.01	1.86
19.50	4.06	2.05	1.80

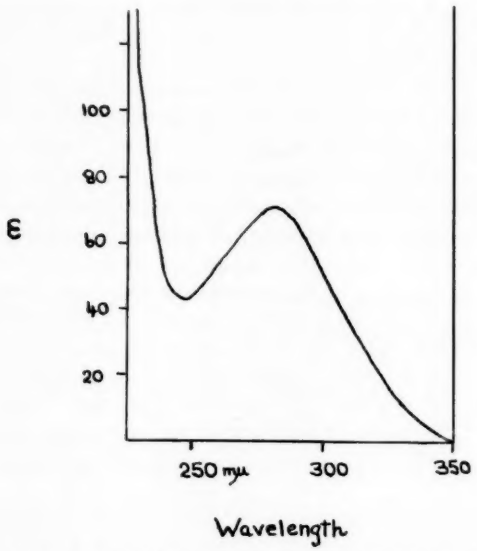


FIG. 1. The ultraviolet absorption spectrum of *erythro*-3-pentulose in water.

Sodium Borohydride Reduction of erythro-3-Pentulose

A portion of the syrup (100 mg) was dissolved in water (3 ml) and the solution was slowly added to a stirred, ice-cold 1% sodium borohydride solution (5 ml). After 1 hour the solution no longer reduced Fehling's solution, and Amberlite IR 120 (H^+) ion-exchange resin was added. The resin was removed by filtration and washed well with water. The filtrate and washings were evaporated to a white residue which was dissolved in methanol and the solution reconcentrated. After three evaporations with methanol, a clear syrup was obtained (95 mg), which partially crystallized. A small volume of methanol was added and the solution was cooled in an acetone – dry ice mixture. The crystals were removed by filtration; m.p. 98–100° C, mixed m.p. with authentic ribitol 99–101° C.

A portion of the syrup (ca. 20 mg) was dissolved in acetic anhydride containing 1% sulphuric acid and the solution was heated on a water bath (80° C) for 4 hours. The reaction mixture was poured into ice water, neutralized with pyridine, and extracted with chloroform. The chloroform extract was washed with dilute sulphuric acid, sodium bicarbonate solution, and water and was dried over anhydrous sodium sulphate. Evaporation of the chloroform left a syrup which was shown to contain ribitol and xylitol penta-acetates by gas–liquid partition chromatography (22).

erythro-3-Pentulose 2,5-Dichlorophenylhydrazone

A solution of the ketose (100 mg) and 2,5-dichlorophenylhydrazine (100 mg) in methanol was allowed to stand in an oven at 80° C. The resulting syrup was dissolved in a small volume of ethyl acetate and chloroform was added until the solution became turbid. Pale yellow crystals (80 mg) were deposited; these were removed by filtration and recrystallized from ethyl acetate – chloroform; m.p. 125–127° C.

Anal. Calc. for $C_{11}H_{14}O_4Cl_2N_2$: C, 42.7; H, 4.5; Cl, 23.0; N, 9.1. Found: C, 42.4; H, 4.8; Cl, 23.0; N, 9.2.

erythro-3-Pentulose was regenerated when the 2,5-dichlorophenylhydrazone was heated with benzaldehyde (cf. Sowden and Fisher (32)).

Periodate Oxidation of erythro-3-Pentulose 2,5-Dichlorophenylhydrazone

The material (8.6 mg) was dissolved in 25% ethanol (20 ml), 0.3 *M* sodium metaperiodate solution (1 ml) was added, and the solution was diluted to 25 ml with water. A bright yellow precipitate, presumably mesoxalaldehyde-2-(2,5-dichlorophenylhydrazone), formed almost immediately and was removed by filtration after 10 minutes. The pale yellow filtrate was used to estimate the periodate uptake and the formic acid and formaldehyde production as previously described. The results are illustrated in Table III.

TABLE III

Periodate oxidation of *erythro*-3-pentulose 2,5-dichlorophenylhydrazone

Time (hour)	Periodate uptake (moles/mole)	Formic acid production (moles/mole)	Formaldehyde production (moles/mole)
0.25	2.16	0.18	1.80
2.50	2.24	0.18	1.71
9.50	2.20	0.22	1.93

The yellow precipitate was recrystallized from aqueous acetone; m.p. 178–185° C. The material was differentiated from hydroxypyruvaldehyde-2-(2,5-dichlorophenylhydrazone), which was obtained by the periodate oxidation of D-fructose 2,5-dichlorophenylhydrazone, by a comparison of their melting points and infrared spectra.

Anal. Calc. for $C_9H_6O_2Cl_2N_2$: C, 44.1; H, 2.5; Cl, 29.0; N, 11.4. Found: C, 44.4; H, 2.6; Cl, 28.5; N, 11.3.

Characterization of Fraction 4 as DL-*erythro-2-Pentulose*

The material (0.58 g) was shown to be homogeneous when examined in solvents *a*, *b*, and *c*. The chromatographic behavior of the sugar was similar to that of *erythro*-2-pentulose, prepared by the epimerization of L-arabinose (33); both gave a red spot with *p*-anisidine (R_{rib} 1.11 in solvent *c*) and a green coloration with orcinol – trichloroacetic acid, which immediately turned pink when oversprayed with aniline phosphate. Paper electrophoresis indicated that the ketose was not *threo*-2-pentulose.

The ketose was estimated by the cysteine hydrochloride – carbazole method (20). The absorption spectrum was measured after 15 minutes and remained unchanged after 2 hours. Authentic *threo*-2-pentulose was also measured by this reaction and the absorption spectrum increased in intensity during the interval (24). The spectra are shown in Fig. 2.

Periodate Oxidation of DL-*erythro-2-Pentulose*

A standard solution of the pentulose was prepared by dissolving the syrup (20 mg) in water in a standard flask (10 ml). An aliquot of the solution (2 ml equivalent to

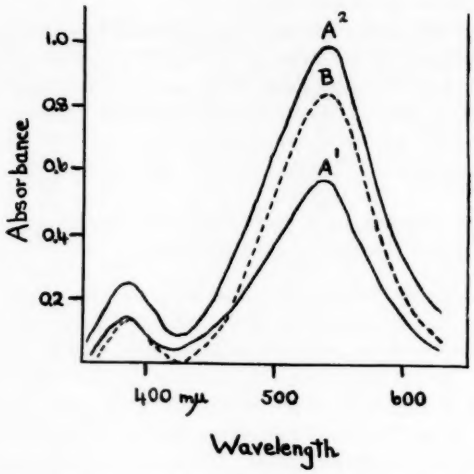


FIG. 2. The visible absorption spectra in the cysteine–carbazole reaction (20) of (A) D-*threo*-2-pentulose (48 γ) after (1) ¼ hour, (2) 2 hours; (B) DL-*erythro*-2-pentulose (43 γ) after ¼ hour and 2 hours.

4.0 mg of ketose) was added to 0.3 *M* sodium metaperiodate solution (0.3 ml) and the solution was diluted to 10 ml with water. The periodate uptake and formic acid and formaldehyde liberation were measured in the manner described previously. The results are shown in Table IV. The oxidation was also performed at pH 8.0 using phosphate

TABLE IV

Periodate oxidation of *erythro*-2-pentulose (unbuffered conditions)

Time (hour)	Periodate uptake (moles/mole)	Formic acid production (moles/mole)	Formaldehyde production (moles/mole)
0.25	1.76	0.95	0.20
6.17	2.06	1.01	0.18
20.0	2.28	—	—

buffer. The periodate uptake and formaldehyde liberation were measured and are recorded in Table V.

TABLE V

Periodate oxidation of *erythro*-2-pentulose (pH 8.0 buffer)

Time (hour)	Periodate uptake (moles/mole)	Formaldehyde production (moles/mole)
0.17	2.43	0.81
0.83	2.72	0.81
2.75	2.91	0.90
7.50	3.01	0.93

Mercuric Acetate Oxidation of Ribitol (Method B)

Ribitol (1.00 g) was added to a solution of mercuric acetate (4.2 g) in methanol (25 ml) containing 1% acetic acid. The solution was refluxed on a hot water bath for

20 hours and the precipitated mercurous acetate (1.8 g) was removed by filtration. The soluble mercury salts were precipitated as their sulphides and the solution was examined by paper chromatography. *erythro*-3-Pentulose and *erythro*-2-pentulose were detected.

2,5-Dichlorophenylhydrazine (0.5 g) dissolved in methanol (10 ml) was added directly to the syrupy mixture (0.90 g) and the solution was evaporated in an oven at 80° C. The syrup was extracted with ethyl acetate and the residual ribitol (0.73 g) was recrystallized from ethanol. Chloroform was added to the ethyl acetate extract and crystalline *erythro*-3-pentulose 2,5-dichlorophenylhydrazone (0.14 g) was obtained; m.p. 124–127° C.

Mercuric Acetate Oxidation of D-*Ribose*

D-Ribose (1.00 g) was oxidized as described for ribitol in method B. The resulting syrup (0.93 g) contained some unreacted ribose and mainly methyl ribonate (detected by paper chromatography). No components corresponding to those obtained in the oxidation of ribitol were detected.

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NOTES

CRYSTAL DATA FOR DIPHENYLARSENICALS

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Very little is known about the detailed structure of arsenic compounds, although it has long been realized that in molecules containing trivalent arsenic the bond arrangement is similar to that found in the layer structure of elemental arsenic (1). The object of the present investigations is to obtain accurate information about the stereochemistry of arsenic by studying compounds containing a variety of substituents; this paper describes the preparation and the determination of the crystallographic data of some diphenylarsenicals.

Bis-diphenylarsenic oxide was prepared from phenyl magnesium bromide and arsenious oxide (2) and recrystallized from 95% ethanol (crystals had m.p. 95°; literature value 92–93°). Chlorodiphenylarsine was obtained by treating the oxide with concentrated hydrochloric acid (2), the resulting oil being separated from the aqueous layer, dried, and purified by distillation at 10^{-3} mm; the fraction boiling at 135–136° was collected. This was a colorless oil which solidified on being cooled in liquid nitrogen, and remained solid on being warmed to room temperature, m.p. 38–40° (lit. value 40–42°). Bromo- and iodo-diphenylarsine were obtained by analogous methods. The bromo derivative boiled at 139–140° (10^{-3} mm) and solidified on being cooled to room temperature. It was recrystallized from 95% ethanol, m.p. 55° (lit. value 52–54°). The iodoarsine was recrystallized from benzene, m.p. 37–39° (lit. value 42–43°).

The unit cell dimensions and space groups of the crystals were determined from single crystal rotation, oscillation, Weissenberg (all with Cu $K\alpha$ radiation, $\lambda = 1.542$ Å) and precession films (Mo $K\alpha$, $\lambda = 0.7107$ Å). These data and other relevant information are given in Table I. Measurement of the densities of the crystals of the halogen derivatives posed a difficult problem, as they were soluble in most organic liquids and were hydrolyzed

TABLE I

Crystallographic data for halogenodiphenylarsines and bis-diphenylarsenic oxide

Formula	$C_{12}H_{10}AsCl$	$C_{12}H_{10}AsBr$	$C_{12}H_{10}AsI$	$C_{24}H_{20}OAs_2$
Molecular weight	264.6	309.0	356.0	474.2
Melting point (deg.)	38–40	55	37–39	95
Crystal system	Monoclinic	Monoclinic	Monoclinic	Monoclinic
a (Å)	11.09	11.00	11.01	11.48
b (Å)	8.55	8.56	8.82	30.2
c (Å)	11.93	12.03	12.34	5.97
β (deg.)	95.0	93.0	91.6	93.8
V (Å^3)	1127	1131	1198	2065
Z	4	4	4	4
D_e (g cm^{-3})	1.550	1.803	1.962	1.516
D_m (g cm^{-3})	~1.5	~1.8	~1.9	1.514
Space group	$P2_1/a$	$P2_1/a$	$P2_1/a$	$P2_1/n$

by water. However, when a crystal was dropped into an aqueous silver nitrate solution of higher density, it floated on the surface for a few seconds, before sinking, which was apparently due to hydrolysis and subsequent coating with silver halide. By making such

observations in aqueous silver nitrate solutions of various densities, it was possible to obtain approximate values for the densities of all three crystals, these measurements being sufficiently accurate to allow estimations of the number of molecules in the unit cells. The density of the oxide was determined accurately by flotation in aqueous $AgNO_3$ solution.

Crystals of chloro-, bromo-, and iodo-phenylarsine are fairly closely isomorphous; the *b*-axis of the iodo derivative is a little longer than the corresponding axes in the other two compounds, and there is a gradual increase in the length of the *c*-axis and a decrease in the value of the β angle on passing from chloro to iodo. The oxide, not unexpectedly, has a different crystal structure. We hope to carry out detailed analyses of some of these structures.

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STERIC CONFIGURATION OF THE ETHER GROUP IN ORTHO ALKOXY AND ARYLOXY BENZOIC ACIDS

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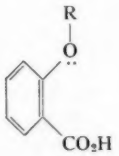
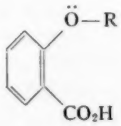
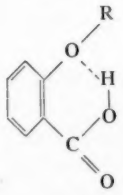
The ether group in ortho alkoxy or aryloxy benzoic acids can assume two configurations (I*a* and I*b*) in which the alkyl or aryl (R) group is directed either away from (as in I*a*) or towards (as in I*b*) the carboxylic acid group. Steric hindrance will be less in the first of these forms, but even so there will be steric crowding between the unshared electrons on the ether-oxygen atom and the carboxylic acid group.



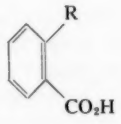
I*a*



I*b*



I*c*



II

The effect of a para substituent can only be electronic, whereas an ortho substituent exerts both an electronic and steric effect. The electronic effects of ortho and para substituents can be assumed to be approximately the same and any differences between them must be primarily steric in origin (1). The ultraviolet spectra of a number of ortho and para alkoxy (I, R = Me, Et) and aryloxy (I, R = Ph) benzoic acids has been measured (Table I) in relation to those of the corresponding alkyl and aryl benzoic acids (II, R = Me, Et, Ph) to determine the magnitude of the ortho steric effect in relation to the configuration of the ethers.

TABLE I

Ultraviolet spectra of benzoic acids*

	λ_{max}, mμ	ε	Δλ,† mμ	ϵ_o/ϵ_p‡
Benzoic	230	10,700§	—	—
o-Methyl	228	5,000§	−2	0.36
p-Methyl	236	14,000§	+6	
o-Methoxy	230	6,200§	0	0.43
p-Methoxy	249	14,000§	+19	
o-Ethyl	227	3,800	−3	0.28
p-Ethyl	236	13,500	+6	
o-Ethoxy	232	7,200	+2	0.44
p-Ethoxy	254	16,600	+24	
o-Phenyl	243	15,300‖	+13	0.58
	277¶	5,600		
p-Phenyl	268	26,600‖	+38	
o-Phenoxy	235	14,200	+5	0.77
	260	4,500		
p-Phenoxy	255	18.400	+25	

*Data refer to ethanol solution.
†Δλ to benzoic acid.
‡Ratio molar extinction coefficients of ortho to para isomers.
§Ref. 5.
‖Ref. 6 gives *o* λ_{max} 245 (11,800), *p* 264.5 (26,000).
¶Inflection.

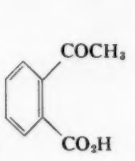
Comparing the methyl and ethyl benzoic acids, it can be seen that an ortho ethyl group, due to the extra carbon and hydrogen atoms, had a greater steric effect since *o*-ethylbenzoic acid showed a slightly hypsochromic shift and the ratio of intensities of ortho to para isomer was much less. However, in the case of the two alkoxy benzoic acids, *o*-ethoxybenzoic acid actually showed a small bathochromic shift, while *o*-methoxybenzoic acid had no displacement with respect to benzoic acid. Moreover, the ratio of the intensities of ortho to para isomers was essentially the same for the methoxy and ethoxy compounds. This similarity in steric effect of the methoxy and ethoxy groups is only possible if the alkoxy benzoic acids assume the configuration I*a*, in which the steric hindrance is due primarily to the unshared electrons on the ether-oxygen atom.

In the cases of the ortho phenyl and phenoxy compounds, the phenyl groups can be better accommodated by twisting of this ring with respect to the other. Nevertheless, the steric hindrance of the phenoxy derivative was much less than for the phenyl compound, again supporting the configuration I*a*.

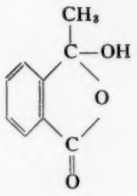
The infrared absorption of *o*-methoxybenzoic acid has been shown to be anomalous (2) since it has a sharp hydroxyl peak at 2.96 μ and the carbonyl peak at 5.76 μ (the para isomer had hydroxyl broad 3.4–3.6 μ and carbonyl at 5.93 μ) and this was attributed to internal hydrogen bonding as in I*c*. *o*-Ethoxybenzoic acid had hydroxyl 2.98 μ medium, 3.4–3.5 μ weak, and carbonyl 5.74 μ strong, 5.91 μ medium, whereas *o*-phenoxybenzoic acid had hydroxyl 2.94 μ weak, 3.4–3.6 μ medium, and carbonyl 5.72 μ medium, 5.88 μ strong (*p*-ethoxy- and *p*-phenoxy-benzoic acids had hydroxyl 3.4–3.6 μ and carbonyl

5.95 μ). This suggests that the amount of the hydrogen-bonded form was less in the case of the *o*-ethoxy acid and still less in the *o*-phenoxy acid, the difference being probably due to the increasing steric size of the substituent.

During the course of this work *o*-acetylbenzoic acid was prepared and it showed λ_{max} 230 mμ, ϵ 10,700,275 (inflection), ϵ 2500 and 282 mμ, ϵ 2400. The main maximum is more characteristic of a benzoic acid (λ_{max} 230 mμ, ϵ 10,000 (1)) than an acetophenone (λ_{max} 240 mμ, ϵ 13,000), although the other maxima are not consistent with the simple structure III*a* and the compound probably exists in solution as the lactol III*b* (cf. phthalide λ_{max} 227 mμ, ϵ 9900; 273, ϵ 1720; and 280, ϵ 1660 (3)). (We are grateful to the referee for pointing out this possibility.) The abnormal infrared carbonyl band (at 5.63 μ) also supports the lactol structure (cf. ref. 4).



III*a*



III*b*

EXPERIMENTAL

Benzoic acids.—*o*-Phenoxybenzoic acid was prepared by treatment of phenyl salicylate with sodium (7) and *o*-phenylbenzoic acid by reaction of fluorenone with potassium hydroxide in diphenyl ether (8).

o-Ethoxybenzoic acid.—Methyl salicylate (40 g) was added to sodium (11 g), dissolved in anhydrous ethanol (150 ml), cooled to 0°, and ethyl sulphate (75 g) added slowly over $\frac{1}{2}$ hour. The reaction was stirred for 2 hours when it became nearly solid and was allowed to stand for 2 days before water and 10% sodium hydroxide were added. The methyl *o*-ethoxybenzoate, b.p. 103–105° at 20 mm, so formed was hydrolyzed by refluxing overnight with 20% sodium hydroxide to give the acid, b.p. 175–178° at 20 mm (9).

p-Ethoxybenzoic acid.—*p*-Hydroxybenzoic acid was esterified by refluxing with ethanol and sulphuric acid in benzene, and azeotropically removing the water formed to give ethyl *p*-hydroxybenzoate, m.p. 116° from ethanol (lit. m.p. 112.5° (10)), which was converted to *p*-ethoxybenzoic acid, m.p. 193° (lit. m.p. 195–196° (11)) as above.

o-Ethylbenzoic acid.—*o*-Acetylbenzoic acid (12 g), prepared from phthalylacetic acid (12), was refluxed with amalgamated granular zinc (30 g) in concentrated hydrochloric acid (60 ml) and water (50 ml) for 8 hours, giving the acid, m.p. 64° from water (lit. m.p. 65° (13)).

p-Ethylbenzoic acid.—Aluminum trichloride (15 g) was added to ethylbenzene (10.6 g) in carbon disulphide (50 ml) cooled to 0° and oxalyl chloride (16 g) in carbon disulphide (50 ml), then added over $\frac{1}{2}$ hour with cooling in an ice–salt bath (14). The reaction mixture was allowed to stand overnight and was decomposed with 10% hydrochloric acid. The product was extracted from the organic layer with 10% sodium hydroxide and liberated by acidification. The product was recrystallized (charcoal) from water to m.p. 114° (lit. m.p. 113° (15)).

p-Phenylbenzoic acid.—This was prepared as above from diphenyl and had m.p. 232° from ethanol (lit. m.p. 228° (16)).

p-Phenoxybenzoic acid.—Similar reaction of diphenyl ether gave *p,p*-diphenoxybenzil, m.p. 125° (from acetic acid), which was oxidized with hydrogen peroxide in boiling acetic acid to *p*-phenoxybenzoic acid, m.p. 161° (from ethanol) (lit. m.p. 160° (17)).

Spectra.—The ultraviolet spectra were determined on 95% ethanol solutions using a Beckman D.U. spectrophotometer. The infrared spectra were determined on solutions in carbon tetrachloride using a Baird-Atomic double beam K.2 spectrometer.

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STABILITY OF $CoBr^+$ AND $NiBr^+$

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In a recent paper (1) one of the present writers reported the stability constants for the formation of the complex ions $CoCl^+$, $NiCl^+$, $CuCl^+$, and $CuBr^+$. Some of these constants, particularly that for $CuBr^+$, showed an anomalous variation with temperature; and although some explanations were suggested, no definite conclusion could be reached. The object of the present note is to report similar measurements for the ions $NiBr^+$ and $CoBr^+$. Previous measurements on nickel bromide have been made by Job (2), who only obtained evidence of $NiBr_2$ with a stability constant of 6×10^{-4} at 18° C. With cobalt bromide he obtained evidence for $CoBr^+$ with a stability constant of 5×10^{-3} at 18° C. References to early semiquantitative work, and work in other solvents, may be found in reference 3.

The present measurements were made by means of cell voltages in a manner very similar to that already described (1). The cell used was Ag, $AgBr/NaBr+M(ClO_4)_2+NaClO_4+HCl_4/NaBr+NaCl_4+HClO_4/AgBr$, Ag. The concentrations of sodium bromide and perchloric acid (about 0.03 *M*) were the same on both sides, as was the ionic strength, which was adjusted to a value of 2.0. Recrystallized 'analar' sodium bromide was used, and other reagents were the same as in the previous work. The electrodes were prepared by the method of Janz and Taniguchi (4). It was checked that the electrodes immersed in two concentrations of sodium bromide gave the calculated voltage over the range 0 to 50° C within 1%.

Since previous work (1) had suggested the possibility of ions of the type M_2X^{+3} (where X is a halogen) measurements were made over a range of concentrations of metal ion

in order to detect ions of this type. In general, all solutions contained high metal and low bromide concentrations, conditions which would favor MBr^+, but it was checked that the calculated stability constants did not vary appreciably with double the concentration of bromide ions. This confirms that the complex ions formed were, in fact, $CoBr^+$ and $NiBr^+$. The results are given in Table I. Most of the voltages in this table are the

TABLE I

A. Nickel bromide

(Total Ni), *M*	(Total Br), *M*	*T*, °C	e.m.f.	K_1
0.0975	0.008096	25	1.800 mv	0.75
0.1394	"	"	2.648	0.78
0.1672	"	"	3.120	0.78
0.2090	"	"	3.826	0.77
0.2413	"	"	4.212	0.74
0.2787	"	"	4.875	0.755
0.1550	0.008260	0	1.620	0.46
"	"	5	1.848	0.52
"	"	10	2.013	0.56
"	"	15	2.200	0.60
"	"	18	2.344	0.635
"	"	20	2.462	0.665
"	"	25	2.774	0.74
"	"	30	2.900	0.76
"	"	35	3.028	0.785
"	"	40	3.108	0.79
"	"	45	3.146	0.79
"	"	50	3.250	0.805
0.3100	0.008000	18	5.048	0.72
"	"	22	5.302	0.75
"	"	30	5.764	0.80
"	"	35	5.777	0.79
"	"	40	5.988	0.805
"	"	50	6.535	8.86
0.0775	0.008000	22	1.367	0.71
"	"	40	1.506	0.735

B. Cobalt bromide

(Total Co), *M*	(Total Br), *M*	*T*, °C	e.m.f.	K_1
0.0580	0.008000	5	0.551 mv	0.40
"	"	10	0.720	0.515
"	"	23.6	0.927	0.64
"	"	30	1.061	0.72
"	"	33.5	1.181	0.795
"	"	40	1.440	0.85
"	"	45	1.486	0.87
0.1160	0.008026	5	1.108	0.41
"	"	10	1.431	0.52
"	"	20	1.923	0.69
"	"	25	2.219	0.78
"	"	30	2.512	0.875
"	"	35	2.590	0.89
"	"	40	2.592	0.875
"	"	45	2.566	0.85
"	"	50	2.545	0.83
0.2320	0.008000	10	2.540	0.475
"	"	15	3.280	0.61
"	"	20	4.058	0.755
"	"	25	4.104	0.755
"	"	30	4.885	0.89
"	"	35	5.102	0.92
"	"	40	5.102	0.885
"	"	45	5.025	0.87
"	"	50	4.926	0.84

average of several measurements. The last column gives the values for the equilibrium constants, $K_1 = [MBr^+]/[M^{++}].[Br^-]$, calculated on the assumption that no other complex is present.

The results give no definite evidence of complexes of the formula M_2Br^{+3}. Although the values of K_1 for $NiBr^+$ are somewhat higher in the series with 0.310 M nickel than with 0.155 M, this trend was not observed in the first series when the nickel concentration was raised gradually from 0.0975 M to 0.2787 M. With cobalt bromide no drift in K_1 was observed with changing cobalt concentration.

The temperature coefficient of K_1 for $NiBr^+$ seems to be larger at low temperatures. ΔH for $Ni^{++} + Br^- \longrightarrow NiBr^+$ appears to fall from about 3 kcal to 0.5 kcal over the range 0 to 50° C. The same trend in an even more marked form was found for $CoBr^+$. A similar situation had been found earlier for $CuBr^+$ from spectrophotometric measurements (1). There is at present no satisfactory explanation of this behavior, though various possibilities were discussed in the earlier paper. One would be inclined to suspect some irregularity in the performance of the silver bromide electrodes, except that these were found to behave as expected in bromide solutions not containing cobalt or nickel, and that the similar behavior of $CuBr^+$ was detected by the spectrophotometer.

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VOLATILITY OF CUPRIC NITRATE

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The volatility of anhydrous cupric nitrate has been reported (1). When hydrated cupric nitrate is ignited the major products are oxides of nitrogen, oxygen, and cupric oxide. If the gases evolved by ignition of hydrated cupric nitrate are piped into the burner of a flame spectrograph, the emission of the green 5105 Å copper line can be detected in the resultant spectrum. In each experiment, care was taken to ensure that the whole apparatus was copper free, and the gases were passed through glass bead filters to remove entrained particles. Blank experiments with aluminum and ferric nitrates in identical apparatus showed no emission at this wavelength due to trace contamination or nitrogen oxides. Similar experiments using calcium and barium nitrates failed to give any spectral emission characteristic of either metal, indicating that the gas filters were effective. It is therefore concluded that small quantities of volatile cupric nitrate are produced during the ignition of the hydrate.

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INVERSE INTERMOLECULAR KINETIC ISOTOPE EFFECTS IN UNIMOLECULAR REACTIONS. DIFFERENTIAL QUANTAL EFFECTS IN THE NON-EQUILIBRIUM BEHAVIOR* †

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Using cyclo-C_3H_6 and -C_3D_6, Blades (1) has determinedthe kinetic isotope effect for C_3H_6 and C_3D_6 structural isomerization (2, 3) near p_∞ as k_H/k_D (60 cm) = 0.82 exp $(1300/RT)$; the ratio declines with pressure (Table I).

To examine this effect, we use the RRK-Marcus formulation (4) with accurate enumeration of densities of harmonic vibrational energy levels (5, 6); over-all rotations are taken as adiabatic and all vibrations active.

$$k_{uni} = \frac{I_r e^{-E_0/kT}}{Q_v h} \sum_{\epsilon^+=0}^{\infty} \frac{\sum_{\epsilon_v^+ < \epsilon^+} P(\epsilon_v^+)\, e^{-\epsilon^+/kT}}{\sum_{\epsilon_v^+ < \epsilon^+} P(\epsilon_v^+)} \Big/ \left(1 + \frac{I_r}{\omega h} \frac{}{N(E_0+\epsilon^+)}\right)$$

where I_r is the inertial and symmetry number ratio, Q_v the molecule vibrational partition function, and $P(\epsilon_v^+)$ the vibrational degeneracy at ϵ_v^+ of the activated complex.

p_∞ Region

The expression for k_∞ is identical with Eyring theory (7). The model for $C_3H_6^+$ depends on the mechanism, that is, whether H migration (3) or ring expansion (or trimethylene formation) with H migration (2, 9). We use the model for $C_3H_6^+$ described previously (9, 10)‖ and, redefining $k_\infty = A\exp(E_a/RT)$, A(calc.) = $10^{15.32}$; A(expt. (8)) = $10^{15.30}$. The calculated isotopic ratio is $(k_H/k_D)_\infty = I_{rH}Q_{vD}Q_{vH}^+ \exp(\Delta E_0/RT)/I_{rD}Q_{vH}Q_{vD}^+ = A_r \exp(\Delta E_a/RT) = 0.88 \exp(1300/RT)$. The I_rQQ^+ ratio, and also A_r, is <1 (although not sufficient to counterbalance the exponential) since $I_{rH}/I_{rD} \simeq 1.00$ while quantal behavior of the loosened complexes is more classical than for the molecules.

p_0 Region

For strong collisions, $k_0 = \omega\int_{E_0}^{\infty} N(\epsilon)\exp(-\epsilon/RT)d\epsilon/Q_v$; at high energies, integration

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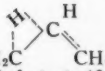
‖The free energy of activation is higher for structural than for geometrical isomerization, and the former transition state is distinct from the latter (2). The complex is represented as  For the alternative H migration mechanism, a ring expansion postulate has also been added (ref. 2, footnote 10) and any difference in complexes is now drastically reduced. In addition to elimination of a C—H stretch, frequency lowerings in $C_3H_6^+$ relative to C_3H_6 correspond principally to a C≡C torsion frequency, C—C twist frequency, and a skeletal bending mode (545 (3) cm^{-1}). The complex assignments obey the frequency–bond order rules, and deviate from the Teller–Redlich product rule by <5%, the exact correspondence depending on the reduced mass factor for the reaction co-ordinate. Proper analysis of the reaction co-ordinate for this drastic intramolecular rearrangement is quite complex. Other definitions of this co-ordinate (cf. F. H. Westheimer, Chem. Revs. **61**, 265 (1961)) could be used to obtain a similar result; bending C—H motion may be introduced. The present semiempiricism (i.e. adjustment to fit the experimental ΔE_a, particularly, while obeying the previously mentioned rules) gives a useful representation of the characteristic frequency pattern of the complex since the calculations do not depend critically on the few uncertainties in frequencies, relative to the large total frequency pattern for all modes active. Molecular frequencies were taken from H. Gunthard, R. C. Lord, and T. R. McCubbin, Jr. (J. Chem. Phys. **25**, 768 (1956)) and grouped (6).

with the correct energy density is proper. The reaction co-ordinate no longer involves $C_3H_6^+$. Then $(k_H/k_D)_0 = \omega_H Q_{vD} \exp(\Delta E_0/RT)R/\omega_D Q_{vH} = 0.25$; R is an integral ratio, and $\Delta E_0 = 1.4$ kcal. Unlike the p_∞ expression for which each energy level sum starts at zero, the integrals here start at higher energies; since the quantal behavior is more classical in C_3D_6, R is $\ll 1$ and outweighs the remaining factor, each ratio of which is >1.

The Fall-off Region

Another aspect of the behavior is this: k_H/k_D should decline as p decreases for the reason, among others, that on the present formulation C_3D_6 is characterized by a classical empirical Kassel (3) s value greater than for C_3H_6, and thus by slower fall-off, since s rises toward the total actual number of active modes as the classical treatment becomes relatively more valid (4, 6). This differential quantal behavior on lowering of frequencies is analogous to the change of non-equilibrium behavior to be expected with temperature rise for a given molecule: the characteristic ratio $h\nu_i/kT$ also decreases with rising T, and the classical s parameter should rise. (The change of fall-off *curvature* accompanying the rise of s is complicated by an opposing temperature effect (11); further discussion will be given elsewhere.)

Experimental fall-off for C_3H_6 at 718° K corresponds (2) to $s = 10.5$ (or Slater $n = 13.5$). The present calculational model gives s (755° K) = 10.3, and s (718°) = 10.0 (the decimals have only qualitative significance). For C_3D_6 at 755° the calculated s is 12.

Table I gives the general isotope comparison. Tunnel effect is not considered. The

TABLE I

Pressure variation of cyclopropane isotope effect (755° K)

p, cm	∞	10^2	10	1	10^{-1}	10^{-2}	10^{-3}	0
$(k_H/k_D)_{exp\ (1)}$		1.96	1.88	1.70	1.50	1.30		
$(k_H/k_D)_{calc}$	2.10	2.08	2.00	1.80	1.50	1.19	0.83	0.25

general agreement is satisfactory. Anharmonicity corrections may also be made; they should not affect the present conclusions significantly. The present case involves a combined primary–secondary isotope effect; some interesting formalism arises concerning possible combinations of primary and secondary effects in unimolecular reactions, and their change between the high- and low-pressure limits.

The inverse intermolecular isotope effect at lower-pressure regions of thermal unimolecular reactions should be of common occurrence. However, the differential divergence of isotopic reactions from classical behavior will depend on the characteristic vibrational frequency patterns and isotopic frequency shifts involved, on the energy range, i.e., on E_0, and on the bonding in the complex. In general, there is little connection between either frequency patterns of molecules or ΔE_0, and critical energies for reaction (6).

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